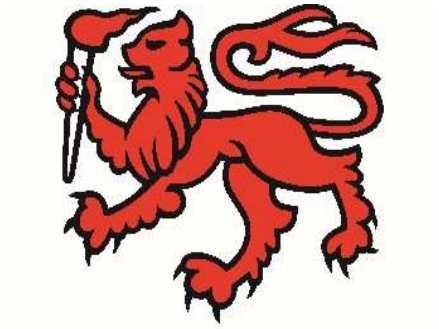

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MORPHOLOGY OF TRUNK MUSCLES AND THEIR POTENTIAL ROLE IN ACTIVE LIVING AND QUALITY OF LIFE OF OLDER ADULTS

By

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DECLARATION OF ORIGINALITY

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by any other person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

William Augusto Cuellar

Date: 04-04-2019

STATEMENT OF ETHICAL CONDUCT

"The research associated with this thesis abides by the international and Australian codes on human experimentation, and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University."

The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the VIDEO study and sub-study, and we obtained written informed consent from all participants. Approval numbers are as follows:

Vitamin D Effect on Osteoarthritis (VIDEO) study:

Ethics approval was received from The Tasmania Health and Human Ethics Committee (reference number H1040).

ClinicalTrials.gov identifier: NCT01176344;

Australian New Zealand Clinical Trials Registry: ACTRN12610000495022.

Protocol

Cao Y, Jones G, Cicuttini F, et al. Vitamin D supplementation in the management of knee osteoarthritis: study protocol for a randomized controlled trial. Trials 2012;13:131.

The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the reproduction of photographs in this thesis that were taken during various stages of dissection (reference number H0017462). The photographs were taken during the development of audio-visual resources for medical students at the school of medicine, College of Health, University of Tasmania. The bodies were kindly donated by community members to the Body Bequest Program at the school of medicine. All donors signed informed written consent for their bodies to be used for medical education and research

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STATEMENT OF CO-AUTHORSHIP

This thesis includes publications for which William Augusto Cuellar (WAC) was not the sole author. William was the first author in the research of each manuscript; however, he was assisted by the co-authors whose contributions are detailed below.

Chapter 3

William A Cuellar, Anitra Wilson, Leigh Blizzard, Peter Otahal, Michele L Callisaya, Graeme Jones, Julie A Hides, Tania M Winzenberg.

Cuellar WA, Wilson A, Blizzard CL, Otahal P, Callisaya ML, Jones G, et al. The assessment of abdominal and multifidus muscles and their role in physical function in older adults: a systematic review. Physiotherapy. 2017;103(1):21-39.

Author contributions

Study conception and design:	TMW, GJ, JAH
Project management of study during implementation:	TMW
Acquisition of data:	WAC, AW, TMW
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Drafting and revisions of manuscript:	WAC, AW, JAH, CLB, MLC, PO, GJ, TMW

All authors critically reviewed and edited the manuscript, read and approved the final version.

Chapter 5

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Author contributions

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Chapter 6

William A Cuellar, Leigh Blizzard1, Julie A Hides, Michele L Callisaya1, Graeme Jones, Flavia Cicuttini, Anita Wluka, Changhai Ding, Tania M Winzenberg

William A Cuellar, Leigh Blizzard1, Julie A Hides, Michele L Callisaya1, Graeme Jones, Flavia Cicuttini, Anita Wluka, Changhai Ding, Tania M Winzenberg. Vitamin D supplements for trunk muscle morphology in older adults: secondary analysis of a randomised controlled trial. Journal of Cachexia Sarcopenia and Muscle 2018;10(1):177-87, DOI: 10.1002/jcsm.12364

Author contributions

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Project management of study during implementation:	TMW, CD, GJ
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Chapter 7

William A Cuellar, Leigh Blizzard1, Julie A Hides, Michele L Callisaya1, Graeme Jones, Flavia Cicuttini, Anita Wluka, Changhai Ding, Tania M Winzenberg. Associations between abdominal and multifidus muscle size and physical activity, physical function and quality of life among adults aged 50-79 years: a cross-sectional study

Author contributions

Study conception and design:	TMW, GJ, JAH, CD, FC, AW
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Acquisition of data:	WAC
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Analysis and interpretation of data:	WAC, LB, JAH, MLC, TMW
Drafting and revisions of manuscript:	WAC, LB, JAH, MLC, GJ, TMW, CD, FC, AW

This manuscript is in the last stages of preparation prior to submission to a peer review journal.

We, the undersigned, agree with the above stated contribution of work undertaken for each of the published (or in preparation) peer-reviewed manuscripts contributing to this thesis:

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ABSTRACT

Background

The muscles of the trunk are essential for an individual's ability to perform normal functional activities such as standing or walking and are involved in the control of balance and posture. Decreased trunk proprioception, muscle imbalance and functional decline of these muscles all have the potential to alter posture and balance, leading to an increase in the risk of falls and deterioration in physical function and quality of life. The trunk muscles investigated in this study are the rectus abdominis, transversus abdominis, internal oblique, external oblique and the lumbar multifidus (MF) muscles. The external and internal abdominal oblique muscles are torque producers of the trunk, while the transversus abdominis and MF muscles are tonically active during weight-bearing activities. While peripheral skeletal muscle mass and strength deteriorate with age (sarcopenia), the effect of ageing or pathology on muscles of the trunk, and the potential effects these changes have on physical function and quality of life are not fully understood.

Aims

This thesis aimed to:

1. Summarise the evidence in older adults for:
    i. changes in function, composition and morphology of the abdominal and MF muscles and the effects of these changes on physical function.
    ii. validity and reliability of electromyographic and imaging measurements of abdominal and multifidus muscles among adults aged 50 years and older.
2. Determine the test-retest reliability of ultrasound imaging (USI) for the assessment of abdominal and MF muscle thickness and CSA at the L2 - L5 vertebral levels in older adults. These results will determine the appropriateness of using these measures in cross-sectional and longitudinal studies (aims 3 and 4), particularly as outcomes for randomised controlled trials (RCT)
3. Determine the effect of 12 months of vitamin D supplementation, on morphology and function of the abdominal and MF muscles of adults aged 50 to 79 years with low serum 25(OH)D levels.
4. Determine the associations between abdominal and MF muscle size and function and measures of physical activity, physical function and quality of life among older adults.

Methods

The first part of this thesis provides a comprehensive and systematic assessment of the current literature investigating abdominal and multifidus muscle in older adults (Study 1). This study helped to inform the studies in the second part of this thesis (Studies 2 – 4) that aimed to fill some of the gaps in the literature identified in the systematic review. Studies 2 - 4 used data from an ultrasound imaging sub-study (n=217) of the Vitamin D Effect on Osteoarthritis (VIDEO) clinical trial, conducted between June 2010 and December 2013. The participants were community-dwelling adults aged 50-79 years with ongoing symptoms of knee osteoarthritis and serum 25(OH)D levels between 12.5 and 60 nmol/L.

Key findings

The key findings and evidence gaps identified by the systematic review (Study 1) were:

- Research on abdominal and MF muscles in older adults was limited
- There was limited evidence that imaging modalities were reliable tools for the assessment of abdominal and MF muscles of older adults
- There was no evidence for the reliability of test-retest measures of abdominal or MF muscles using ultrasound imaging in older adults
- There was limited evidence for an age-related decrease in abdominal and MF muscle size and an increase in intramuscular fat infiltrations that had the potential to affect physical function of older adults
- There was limited, but consistent evidence of detrimental effects on abdominal and MF muscles by conditions that affect physical function such as various spinal conditions and low back pain (LBP)
- There was limited or no evidence on the effect of other conditions such as stroke or vitamin D deficiency on abdominal or MF muscles
- There were no studies in healthy, older adults investigating associations between trunk muscle measures and any aspect of physical activity or physical function nor identifying modifiable factors that could mitigate age-related changes in abdominal or MF muscles

Study 2 determined the test-retest reliability for measurements of abdominal and MF muscle thickness and CSA. The estimates of reliability were as follows:

- Substantial (ICC 0.87-0.98) for all measurements of abdominal muscles, except for the right internal oblique muscle in the contracted state which was moderate (ICC 0.75)
- Substantial (ICC 0.84-0.91) for all measurements of MF muscle CSA

- Fair to moderate (ICC 0.55-0.74) for all measurements of MF muscle thickness

Establishing the test-retest reliability of USI for assessing abdominal and lumbar multifidus muscles confirmed the appropriateness of using these measures in longitudinal studies and particularly as outcomes for randomised controlled trials (RCT)

We used this technique to assess muscle outcomes in the VIDEO RCT. Twelve months of vitamin D supplementation in vitamin D deficient older adults with knee osteoarthritis alone was not an effective means to improve or maintain abdominal or MF muscle size of active, community dwelling adults aged 50-79 years (Study 3).

Given the lack of effect of vitamin D on muscle size, we proceeded to investigate another important gap in the literature described in section 1.4 of the introduction of this thesis and also identified the systematic review, namely a paucity of studies investigating associations between trunk muscle measures and any aspect of physical function in healthy older adults. This cross-sectional analysis revealed no cross-sectional correlations between abdominal or MF muscle size or function (assessed by changes in muscle thickness on contraction) and measures of physical activity (International Physical Activity Questionnaire and pedometer), physical function (functional deficit subscale of the Western Ontario and McMaster Universities Arthritis Index and quality of life (Assessment of Quality of Life instrument) in healthy, active, community-dwelling adults with knee osteoarthritis (Study 4). However, such effects cannot be ruled out due to the limitations in the measures used to assess muscle function, physical activity and physical function available in VIDEO.

Conclusion

Age and various spinal conditions have detrimental effects on abdominal and MF muscle size, strength, activation and muscle quality, reflected in an increase in intramuscular fat infiltrations. However, how these detrimental factors affect physical function and healthy ageing are not clearly understood. The findings in this thesis have contributed to fill some of the identified gaps in the literature.

Particularly important are the finding of the RCT on the effect of vitamin D supplementation on abdominal and MF muscles suggesting that vitamin D supplementation alone is not an effective therapy to improve or preserve the size or ability to contract of postural muscle of the trunk. A question that was not investigated in this study and remains unanswered is the effect of vitamin D supplementation on other aspects of trunk muscle function such as strength, power or physical function.

Study 4 contributed to a limited body of evidence on the associations between abdominal and MF muscle size and measures of physical function. Although our negative results are consistent with findings in the systematic review published in 2017 and some of the studies in the systematic review update in this thesis, the evidence is not robust enough to rule out associations between abdominal and MF muscle size and measures of physical function in older adults. Given that the evidence base remains limited, further research is definitely required, to further address important persisting gaps in the literature. These include:

- what other factors affect trunk muscles of older adults?
- what are the long-term effects of declines in muscle size on physical activity, physical function and quality of life of older adults?
- what strategies can be implemented to mitigate the effect of age-related changes on these muscles?

Finally, the literature in the systematic review update suggest that abdominal and MF muscle strength and muscle quality are important determinants of physical function in older adults. Therefore, these two areas of research would also appear to be promising for future research investigating the effect of age-related changes in abdominal and MF muscles on physical function and quality of life of older adults.

DEDICATION

I dedicate this thesis to my mother (Late) Mrs. Sunilda Pardo de Cuellar who died without fulfilling her dream of seeing one of her children become a doctor.

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This is the culmination of a very unlikely journey that started more than 30 years ago in Bogota, Colombia. I will be eternally grateful to my best friend Bernardo Gonzalez who made it possible for me to be in this country. He has always been there at all the significant events in my life, encouraging me along and reminding me how far our childhood dreams have taken us.

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LIST OF PUBLICATIONS

Publications arising from this thesis:

Cuellar W, Wilson A, Blizzard C, Otahal P, Callisaya M, Jones G, et al. The assessment of abdominal and multifidus muscles and their role in physical function in older adults: a systematic review. Physiotherapy. 2017;103(1):21-39.

Cuellar WA, Blizzard L, Callisaya ML, Hides JA, Jones G, Ding C, et al. Test-retest reliability of measurements of abdominal and multifidus muscles using ultrasound imaging in adults aged 50-79 years. Musculoskelet Sci Pract. 2017;28(e1-e88):79-84.

William A Cuellar, Leigh Blizzard1, Julie A Hides, Michele L Callisaya1, Graeme Jones, Flavia Cicuttini, Anita Wluka, Changhai Ding, Tania M Winzenberg. Vitamin D supplements for trunk muscle morphology in older adults: secondary analysis of a randomised controlled trial. Journal of Cachexia Sarcopenia and Muscle 2018;10(1):177-87. DOI: 10.1002/jcsm.12364

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Manuscripts submitted during candidature, external to this thesis material and currently under review

Sadhishaan Sreedharan, Richard Ross, Jens J Froelich, William A Cuellar, Siddharth Karanth. The free extensor retinaculum composite flap. Submitted to the Australasian Journal of Plastic Surgery.

Derek L Choi-Lundberg, Hayder A Al-Aubaidy, John R Burgess, Christine A Clifford, William A Cuellar, Judi A Errey, Amanda J Harper, Roslyn C Malley, Renee M Ross, Anne-Marie M Williams, and Richard Hays. Minimal effects of reduced teaching hours on undergraduate medical student learning outcomes and course evaluations. Submitted to the Medical Teacher Journal

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

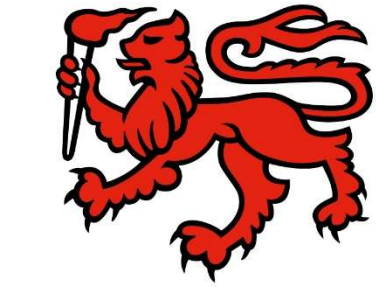
LIST OF ABBREVIATIONS

1,25(OH)2D	1,25-dihydroxyvitamin
25(OH)D	25-hydroxyvitamin D
ACR	American College of Rheumatology
ADL	Activities of Daily Life
AQoL	Assessment of Quality of Life
ASD	Adult Spinal Deformity
ASIS	Anterior Superior Iliac Spine
AW	Anitra Wilson
BBS	Berg Balance Scale
BMI	Body Mass Index
CSA	Cross-Sectional Area
CT	Computed Tomography
EMG	Electromyography
EO	External Oblique muscle
EWGSOP	European Working Group on Sarcopenia
GH	growth hormone
HIV	Human Immunodeficiency Virus
HU	Hounsfield Units
ICC	Intraclass Correlation Coefficient
IO	Internal Oblique muscle

ISI	International Sarcopenia Initiative
IPAQ	International Physical Activity Questionnaire
IWGS	International Working Group on Sarcopenia
LAMT	Lateral Abdominal Muscle Thickness
LBP	Low Back Pain
LSS	lumbar Spinal Stenosis
MA	Muscle attenuation
MDC	minimal detectable change
MET	Metabolic Equivalent of Task
MF	Lumbar Multifidus Muscles
MRI	Magnetic Resonance Imaging
NHMRC	Australian National Health and Medical Research Council
ODI	Oswestry Disability Index
QL	Quadratus Lumborum
RA	Rectus abdominis
RCTs	Randomised Controlled Trials
SB	Sedentary Behaviour
SEM	Standard Error of Measurement
SMD	Standard Mean Difference
SPPB	Short Physical Performance Battery
TLF	Thoracolumbar Fascia
TrA	Transversus Abdominis muscle

TUG	Timed Up and Go test
TW	Tania Winzenberg
USI	Ultrasound Imaging
VAS	Visual Analogue Scale
VIDEO	Vitamin D Effect on Osteoarthritis
WAC	William Cuellar
WOMAC	Western Ontario and McMaster Universities Arthritis Index

CHAPTER 1 – SARCOPENIA, MUSCLES OF THE TRUNK AND VITAMIN D



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Overview

By 2050, the global population of people aged 60 years and over will double, and the number of people over 80 years will triple [1]. This will have profound consequences on social-support systems and health budgets [2]. The Australian government spent an estimated $45 billion on patients admitted to hospitals between 2012 and 2013 and approximately $17 billion in aged care between 2015 and 2016 [3]. The largest growth in population over the period between 2005 and 2013 was among people over 60 years of age, which was the group that accounted for the greatest growth in health expenditure [4].

Physical capacity, skeletal muscle mass and strength [5] deteriorate with age, increasing the risk of falls that could lead to an increase in hospital admissions and health expenditure. Therefore, it is important to focus on this ageing population to identify and develop cost-effective interventions to address both the increase in age-related injuries and the rising costs of health care [6, 7]. The muscles of the trunk have the potential to play a key role in maintaining people's physical capacity due to the complex role these muscles play in load transfer from the upper limbs to the pelvis, force dissipation, control of balance and posture, and movement of the trunk and pelvis [6, 8, 9]. Decreased trunk proprioception [10], muscle imbalance or functional declines of these muscles have the potential to alter posture and balance, increasing the risk of falls that could lead to deterioration in physical function and quality of life [11-15].

Therefore, this thesis examines the effects of ageing on trunk muscles and the implications of this for healthy ageing. It also explores potential factors that might slow age-related changes in these muscles, namely physical activity and vitamin D supplementation.

This chapter discusses

1. Sarcopenia: the age-related process of decline in neuromuscular function and physical performance characterised by a progressive and generalised decrease in lean muscle mass, peripheral muscle size and the consequent loss of muscle strength and muscle function.
2. Muscles of the trunk: . The trunk provides proximal stability for the distal mobility and function of the limbs and its muscles are anti-gravity muscles, crucial for people to be able to perform fundamental functional activities of daily living due to the complex role they play in body load transfer, force dissipation, control of balance and posture, and movement of the trunk and pelvis. The movement producing elements of the trunk

include the muscles of the back, the small intersegmental muscles that provide stability of the spine, the muscles of the thorax that include muscles of respiration and upper limb movement, as well as the muscles of the abdomen and pelvis that produce intra-abdominal pressure.

3. Vitamin D: Vitamin D plays an important role in muscle metabolism, development and growth. vitamin D and its effect on skeletal muscle will be discussed.

1.1 SARCOPENIA

1.1.2 Introduction

Sarcopenia is an age-related process of decline in neuromuscular function and physical performance characterised by a progressive and generalised decrease in skeletal lean muscle mass, appendicular muscle size and the consequent loss of muscle strength and muscle function [16-18]. This is associated with deterioration in physical activity, physical function and quality of life in older adults [11, 12, 17, 19, 20]. Sarcopenia has been described as a key contributor to the risk of falls, frailty, loss of independence and disability in older adults [16, 21-27].

1.1.3 Definition of sarcopenia

Historically, sarcopenia was defined as an appendicular skeletal muscle mass divided by height in square meters that is more than two standard deviations less than the normal mean in younger persons [28, 29]. However, following ongoing criticism [20, 28-33] and in order to provide a better definition and to provide general guidance on the subject, a number of working groups on sarcopenia have been formed around the world [22, 34-37].

Currently, there are three main approaches for definition and diagnosis of sarcopenia:

1- *The European Working Group on Sarcopenia* (EWGSOP2) (2018) [38] recently reviewed their position based on current literature and proposed the following operational definition for the diagnosis of sarcopenia in older individuals following three criteria:

a. Low muscle strength
    - Grip strength: <27 kg for men and <16 kg for women
    - Chair stand: >15 seconds for five rises
b. Low muscle quantity or quality

- Appendicular skeletal muscle mass: <20 kg for men and <15 kg for women
- Skeletal muscle mass index: <7.0 kg/m^2 for men and <6.0 kg/m^2 for women

c. Low physical performance

- Gait speed: ≤0.8m/s
- Short physical performance battery: ≤0.8 m/s
- Timed up and go test: ≥20 seconds
- 400 m walk test: non-completion or ⩾6 min for completion

2- *The International Working Group on Sarcopenia* (IWGS) (2011) [36] proposed a diagnosis of sarcopenia as having a low whole body or appendicular fat-free mass together with poor physical functioning:

a- Low lean mass < 20th percentile of measurement of younger adults. Objective cut points for lean mass in men ≤7.23 kg/m^2 and in women ≤5.67 kg/m^2.

b- Poor physical functioning includes patients who are bedridden, non-ambulatory or unable to rise from a chair unaided. If patients are ambulatory, a gait speed of <1m/s is considered a positive finding.

3- *The Foundation for the National Institutes of Health Sarcopenia Project* [35] proposed the following operational definitions of sarcopenia:

a- Weakness and low lean mass: grip strength < 26 kg in men and <16 kg in women. Lean mass in men <0.789 ALM/BMI and in women <0.512 ALM/BMI.

b- Slowness with weakness and low lean mass: gate speed ≤ 0.8 m/s. Grip strength < 26 kg in men and <16 kg in women. Lean mass in men <0.789 ALM/BMI and in women <0.512 ALM/BMI.

4- *In 2018, the EWGSOP [22] definition of sarcopenia was adopted for use in Australia and New Zealand by researchers and clinicians [39]*

1.1.4 Prevalence of sarcopenia

The different approaches used to define sarcopenia, differences in the populations studied, and methods used to measure lean muscle mass, strength and physical performance have resulted in broad variations in estimates of prevalence for sarcopenia. A study by Baumgartner et al. [28] was one of the first epidemiological studies on the prevalence of sarcopenia. Using data from the New Mexico Elder Health survey and lean muscle mass alone to define sarcopenia, Baumgartner et al. [28] reported rates of sarcopenia between 13.5% - 36.4% in Hispanic and non-Hispanic individuals under the age of 70 years and a much larger prevalence of up to 60% in people older

than 80 years [28]. In a systematic review published in 2014 that included 18 prevalence studies, the prevalence of EWGSOP-defined sarcopenia ranged from 1 – 29% for community-dwelling older adults, 14 – 33% for people in long-term care institutions and was 10% for people in acute hospital care [34].

1.1.5 Aetiology of Sarcopenia

The process by which loss of lean muscle mass occurs is complex and results from the accumulation of several factors associated with ageing [5, 40, 41]. Potential mechanisms include decreased neurological input to muscle (loss of Alpha- motor neurones input to muscle that occurs with ageing) [33], age-related body composition changes [11], systemic low-level inflammation and a decline in endocrine function [16, 42], decreases in food and protein intake [43] and decreased physical activity either due to inactivity or disability [20]. These potential mechanisms are discussed in more detail in the next sections

1.1.5.1 Decreased neurological input

The decrease in strength seen with ageing may be due to impairment of the regeneration capabilities of muscle fibres or an alteration to neural input [17, 44]. An age-related decrease in functional motor neurones innervating muscle [45] leads to a decrease in co-ordinated muscle function [31, 43]. Roubenoff [20] proposed that the continuous loss of alpha motor neurones through life causes motor units to be bigger and have decreased neural input to muscle. Neural input is essential for normal muscle function and age-related neuronal death leads to atrophy, loss of muscle mass and decreased muscle force in older adults [20, 33, 45], which are critical features of sarcopenia [17, 42].

1.1.5.2 Age-related changes in skeletal muscle composition

Although the composition of skeletal muscle varies greatly depending on age, obesity and presence or absence of disease [46], a typical muscle is composed of water (79%), collagenous protein fraction (15%), collagen (3.4%), lipids (2%), other factors (0.6%) [47]. Upper and lower limb skeletal muscle mass peaks in early adulthood [11, 19] and gradually declines by 30% between the ages of 20 and 80 years [48]. Age-related decreases in muscle mass are often associated with increased accumulation of intramuscular fatty infiltrations in skeletal muscle and have been associated with decreases in muscle strength [17, 46]. Decreases in slow twitch, fatigue resistant, Type I and accelerated loss of fast twitch, Type II muscle fibres with ageing have been linked to changes in muscle function associated with decreases in the capacity of older adults to

perform activities such as rising from a chair, climbing stairs and impaired balance [20, 31, 49].

1.1.5.3 Systemic low-level inflammation and endocrine dysfunction

Skeletal muscle mass is maintained by a dynamic balance between muscle protein synthesis from amino acids and muscle protein breakdown [31, 50]. Ageing is associated with both a decline in expression of hormonal factors that stimulate protein synthesis and a rise in the expression of endocrine and inflammatory factors that promote protein breakdown [31]. Similar decreases in protein synthesis and increase in protein degradation are seen in acute illness and chronic inflammatory conditions such as cachexia and human immunodeficiency virus (HIV), which has led to the theory that ageing is associated with a subclinical inflammatory state which increases the production of inflammatory cytokines that in turn increases the rate of muscle catabolism leading to sarcopenia [20, 31]. Declines in growth hormone (GH), testosterone and oestrogen seen with ageing [40] have the potential to affect muscle mass and function leading to sarcopenia [42]. A progressive decline in GH begins in the fourth decade and has been proposed as an important mechanism for the loss of lean muscle mass and muscle function [31, 42].

1.1.5.4 Decreases in food and protein intake

There is an age-related decrease in food intake in the general population and in healthy older adults [51]. The reasons for this decline in food consumption are complex and include early satiation due to the inability of the gastric fundus to relax and adapt to food intake, and increased release of cholecystokinin and leptin that are associated with decreased food and protein intake [43, 51]. Decreased protein intake often precedes weight loss in the elderly, leading to a loss of both fat and lean muscle mass. In some instances, it causes loss of lean muscle mass only, leading to fat-frailty or sarcopenic obesity [16, 43, 52].

1.1.5.5 Vitamin D deficiency

The association between vitamin D deficiency and the development of sarcopenia has not been clearly established. However, the age-related decline in muscle mass, muscle strength and physical performance coincide with an age-related decrease in the skeletal muscle vitamin D receptor expression. Common clinical symptoms of vitamin D deficiency in older adults include symmetrical proximal muscle weakness, easy fatigability, decreased physical function and increased postural sway [53-61], which is positively associated with balance and risk of falling [62]. Previous reports indicating that higher serum vitamin D levels are associated with greater muscle mass and predictive of increased muscle strength and function in older adults [63], suggest

vitamin D could play a part in the occurrence and progression of sarcopenia [63]. Vitamin D and its effect on skeletal muscle will be discussed in more detail in the third section of this chapter.

1.1.5.6 Decreased physical activity

There is a trend in developed societies towards a decrease in physical activity with increasing age [20]. Various studies have found a correlation between decreased physical activity and the development of sarcopenia [11-15]. Reduced physical activity may lead to increased accumulation of intramuscular fat [41, 64, 65], as well as greater muscle loss compared with physically active adults [20]. There are significant associations between decreased physical activity in older people and increases in body fat measures [66], as well as decreases in lean muscle mass [17, 20, 28, 67]. Along with decreased physical activity with ageing, there is an increase in sedentary behaviour (SB), defined as waking activities with an energy expenditure of ≤1.5 metabolic equivalent of task (MET), while sitting or reclining [68]. In older adults, SB has been associated with decreased or loss of physical function and increased difficulty performing activities of daily life (ADL) [69-72].

1.1.5.7 Muscles investigated to determine sarcopenia

Given that sarcopenia is associated with deterioration in physical activity, physical function and quality of life in older adults [11, 12, 17, 19, 20], muscles of the upper (grip strength) and lower (quadriceps and calves) limbs have been used to quantify loss of strength, muscle mass and physical impediments [38]. Assessments of these muscles have been shown to be valid, reliable and apart from imaging tests, they are easy to use in clinical practice [38]. Assessment of muscles of the trunk or quantification of their qualities are not part of any of the current guidelines for the diagnosis of sarcopenia, despite these muscles playing a key role in body load transfer, force dissipation, control of balance and posture, and movement of the trunk and pelvis. A possible explanation for the omission of the muscles of the trunk in the overall picture of sarcopenia may be that, as is the case for the psoas muscle [38], these muscles have been considered minor muscles and not representative of an overall picture of sarcopenia. The increase use of ultrasound imaging (USI) in clinical practice may facilitate the inclusion of these muscles in the diagnosis of sarcopenia, but studies are needed to ascertain the viability of using this assessment method and the framework it will operate in.

1.1.6 Concluding Comments

This section described sarcopenia as an age-related process characterised by a generalised

decrease in lean muscle mass, appendicular muscle size and the consequent loss of muscle strength and muscle function [16-18]. It also discussed its prevalence and aetiology which include neurological, body composition, endocrine, decreased nutrition and physical activity factors associated with ageing [11, 16, 20, 33, 42, 43].

In the next section, the muscle of the trunk will be described and the essential role these muscles play in an individual's ability to perform normal functional activities will be discussed.

1.2 THE MUSCLES OF THE TRUNK

1.2.1 Introduction

Topographical anatomy divides the human body into segments and focuses its study on specific parts or regions, exploring the organisation and systemic structures within the segment [73]. These segments include the head, neck, upper and lower limbs and the trunk. The trunk provides proximal stability for the distal mobility and function of the limbs [74], and plays a fundamental role in a person's ability to perform activities of daily living through its involvement in load transfer, force dissipation, control of balance and posture, and trunk and pelvic movement [6, 8, 9]. The trunk is subdivided into thorax, abdomen, back and pelvis [73]. The structural musculoskeletal elements of the trunk include the spine, pelvis and the thoracic cage [74] and the connecting soft tissue surrounding these structures. The movement-producing elements of the trunk include the muscles of the back, the small intersegmental muscles that provide stability of the spine, the muscles of the thorax that include muscles of respiration and upper limb movement, as well as the muscles of the abdomen and pelvis that produce intra-abdominal pressure [75-77].

1.2.2 Classification of trunk muscles

For the purpose of mechanical modelling of the spine, Bergmark [9] proposed the concept of local and global systems composed of muscles and intra-abdominal pressure. He defined the muscles with origin or insertion at the vertebra, except for the psoas, as belonging to the local system. The muscles which transfer loads between the thoracic cage and the pelvis and function primarily as movement producers, he assigned to the global system [9]. Even though this classification has been extensively used by researchers and clinicians to describe these muscles,

and various adaptations have been made to this classification [9, 74, 78-83], it does not include some important muscles of the trunk.

In this thesis, the current anatomical classification of the muscles of the trunk will be followed [73, 84]. The muscles of the back are arranged in layers that divide them into intrinsic and extrinsic muscles. The extrinsic (superficial) muscles of the back (trapezius, latissimus dorsi, levator scapulae and rhomboids) connect the upper limb to the axial skeleton and almost all are innervated by the ventral rami of cervical spinal nerves [73, 84]. Although these muscles are located in the back, the primary functions of these muscles are the production and control of movements of the upper limb, and therefore these muscles are instead described as upper limb muscles instead [73, 84]. The serratus posterior muscles, also part of the extrinsic back muscles, are accessory respiratory muscles [73, 84]. The intrinsic or "muscles of the back proper" [73] are the deep muscles of the back that are further divided into superficial, intermediate and deep layers. These muscles are innervated by the dorsal rami of the spinal nerves and their primary function is to maintain posture and produce and control movement of the vertebral column [73]. The terms "trunk muscles" and "muscles of the trunk" will be used interchangeably throughout this thesis and the muscles being referred to here will be the abdominal muscles and the muscles of the intermediate and deep layers of the intrinsic back muscles. The term excludes the extrinsic muscles of the back, the pectoral and intercostal muscles.

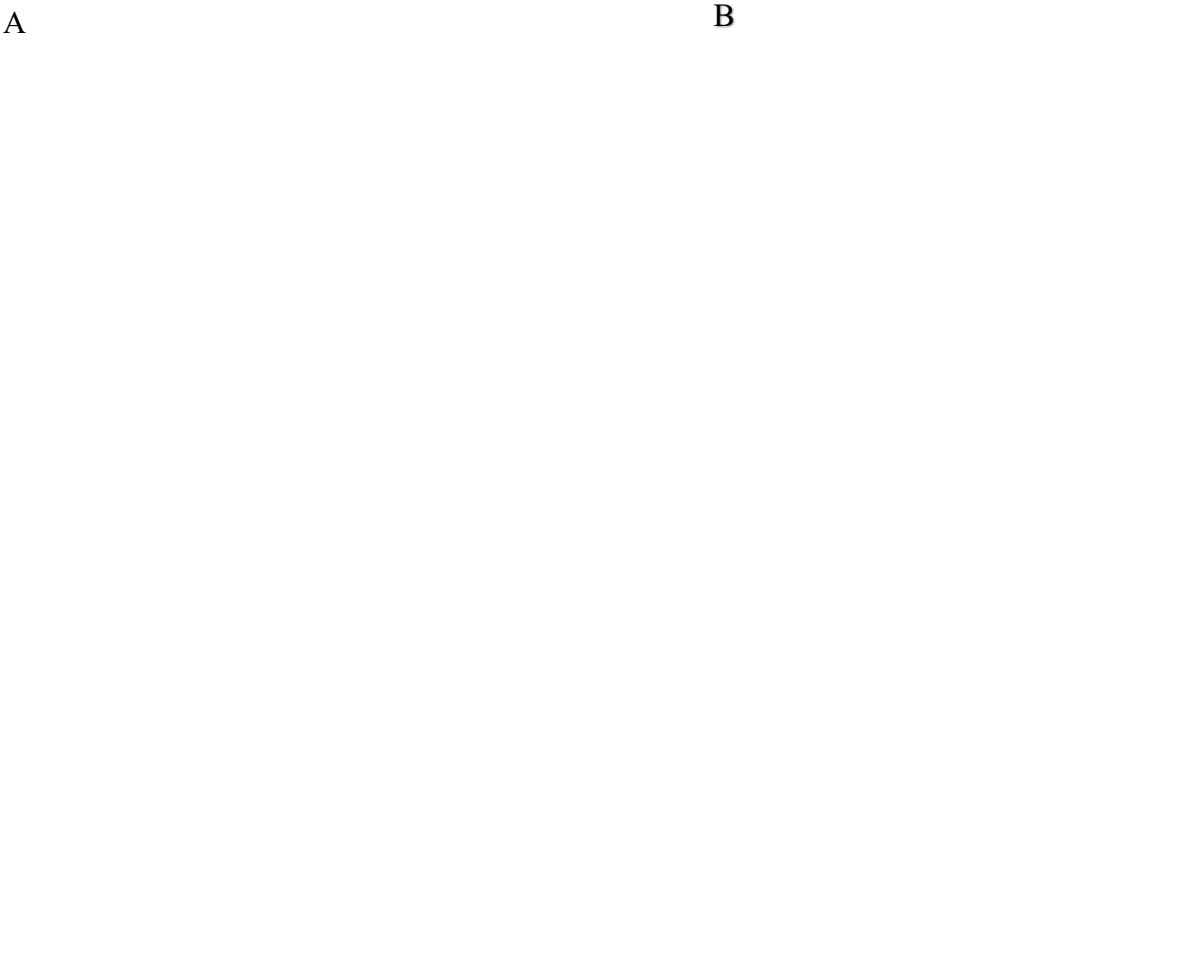
1.2.3 Muscles of the abdominal wall

The rectus abdominis muscle (RA) (Figure 1.1) extends along the entire length of the anterior abdominal wall. The paired muscles are separated in the middle by the linea alba (Figure 1.1). The RA muscle arises from tendons extending from the pubis and inserts as three slips of muscle into the fifth, sixth and seventh costal cartilages and in some instances to the third, fourth and fifth ribs [73, 85, 86]. The RA muscle is fundamentally a trunk flexor [87], and contributes little to spinal compression in lifting and quiet breathing [88]. The RA muscle has phasic electrical activity that is detected before major activity of the back muscles, and exerts stabilising flexion forces to the trunk during walking [89]

Photographs of dissected cadavers from page 10-23 have been removed from the publicly available version at the request of the author, for sensitivity reasons.

Figure 1.1. The rectus abdominis muscle

A B



Images of the anterior abdominal wall. A: on the right, the aponeurosis where the upper and middle fibres of the external oblique muscle insert is labelled. On the left, is the rectus sheath. B: on the right, are the different sections of the rectus abdominis muscle separated by tendinous intersections. (Ethics reference number H0017462)

The external abdominal oblique (EO) muscle (Figure 1.2) is the largest and the most superficial of the abdominal wall muscles. It arises from the external surfaces and the inferior border of the lower eight ribs and curves around the lateral and anterior aspects of the abdomen. The middle and upper fibres insert in the anterior aponeurosis. The inguinal ligament is formed by the margins of the aponeurosis of EO extending between the anterior superior iliac spine (ASIS) and the pubic tubercle [73, 85, 86]. The main action of EO is torque production, especially trunk rotation and flexion [90].

Figure 1.2. The external oblique muscle

Image of the lateral abdominal wall. Labelled is the most superficial of the lateral abdominal muscles, the external oblique and inferiorly where it forms the inguinal ligament. Note the orientation of the muscle fibres. (Ethics reference number H0017462)

The internal abdominal oblique (IO) muscle (Figure 1.3) is the middle layer of the lateral abdominal muscles. It arises from the inguinal ligament, the iliac crest, and posteriorly the thoracolumbar fascia (TLF) [85, 86, 91, 92]. It inserts into the inferior borders of the lower three or four ribs and anterior aponeurosis. The IO muscle is both a postural muscle because it fires together with the transversus abdominis muscle in anticipation of movement, during changes in posture and during expiration [93, 94], and a torque-producing muscle because it is involved in trunk flexion and rotation [95] and compression of the sacroiliac joint [96, 97].

Figure 1.3. The internal oblique muscle.

The image shows muscles of the lateral abdominal wall with cut edges of the external oblique muscle reflected upwards and downwards, revealing the internal oblique muscle. Note the difference in orientation of the muscle fibres compared with the external oblique (Figure 1.2). (Ethics reference number H0017462)

The transversus abdominis (TrA) muscle (Figure 1.4) is the deepest of the lateral abdominal muscles. Its name is derived from the direction of its fibres. It arises from the inguinal ligament, the iliac crest, the cartilages of the lower six ribs, the diaphragm and from the thoracolumbar fascia [85, 86, 91, 98]. The lower fibres of the TrA fuse together with the lower fibres of the IO muscle to form the inguinal aponeurotic flax or conjoint tendon [73, 85, 86, 91, 92, 96]. Throughout the rest of its extent, the aponeurosis passes horizontally and inserts into the linea alba. The TrA muscle has been described as sometimes being fused with the IO muscle or on rare occasions absent altogether [85]. Between the inner surface of the TrA and the extraperitoneal fat there is a thin layer of connective tissue, the transversalis fascia. The transversalis fascia is continuous with the anterior layer of the thoracolumbar fascia posteriorly, the iliac and pelvic fasciae inferiorly and the fascia covering the inferior surface of the diaphragm superiorly [84]

The TrA is an important muscle of respiration. The activity of the TrA and IO muscle increases with increased physical demand

Figure 1.4. The transversus abdominis muscle.

A

B

Image A: shows the three layers of the lateral abdominal muscle group (from superficial to deep: external oblique, internal oblique and transversus abdominis. Image B: shows the transversus abdominis muscle with the external and internal abdominal oblique muscles removed. Note the difference in orientation of the muscle fibres compared with external abdominal oblique (Figure 1.2) and internal abdominal oblique muscles (Figure 1.3). (Ethics reference number H0017462)

The quadratus lumborum (QL) (Figure 1.5) is a large, generally thin, quadrilateral muscle located on the posterior abdominal wall with a combination of various oblique and longitudinal fibres that connect the lumbar transverse processes, the ilium and the 12th rib [85, 86, 98]. The QL

muscle divides into three components (inferior oblique, superior oblique and longitudinal) named after the orientation of its fibres. The longitudinal and oblique fibres attach laterally to the 12th rib and are thought to stabilise the 12th rib during respiration. The remaining fibres attach to the ilium and the upper four lumbar transverse processes and are thought to be weak lateral flexors of the lumbar spine.

Figure 1.5. The quadratus lumborum, iliacus and psoas major muscles

A B

Anterior view of the posterior abdominal wall. Labelled from lateral to medial the iliacus, quadratus lumborum and psoas major muscles. (Ethics reference number H0017462)

1.2.4 The intrinsic muscles of the back

The intrinsic muscles of the back are comprised of three layers: superficial, intermediate and deep.

1.2.4.1 The superficial layer

The splenius muscles are the thick, flat muscles on the lateral and posterior aspects of the neck. The splenius capitus takes origin from the mastoid process and occipital bone and insert into the

spinous processes of the seventh and upper three or four thoracic vertebrae [73, 84]. The splenius cervicis arises from the atlas and axis and inserts into the spinous processes of the third to sixth thoracic vertebrae. These muscles cover and keep in place the deep muscles of the neck. Unilaterally, they rotate the upper cervical vertebrae and head and together they extend the upper cervical spine [73, 84]

1.2.4.2 The intermediate layer: The erector spinae muscles

The erector spinae (ES) (Figure 1.6) is a large musculotendinous mass that varies in size and structure at different parts of the vertebral column [84]. The ES is divided into three muscular columns, each one defined by the superior attachment of their fascicles and the regional areas they traverse. They are named from medial to lateral: the spinalis (thoracis, cervicis and capitus), longissimus (capitis, cervicis, thoracis and lumborum) and iliocostalis (cervicis, thoracis and lumborum) muscles. The erector spinae muscle arises from the iliac crest and sacrum and the different columns may insert into the spine, the ribs or mastoid process of the temporal bone. The three muscular columns are clearly defined in the thoracic region (Figure 1.6), with the spinalis muscle also having fascicles that attach to the first two lumbar vertebrae [73, 84].

Figure 1.6. The erector spinae muscles

Image of the intrinsic, intermediate layer of muscles of the back. Labelled are the three components of the erector spinae muscle at different spinal levels – Iliocostalis lumborum, longissimus thoracis and spinalis muscles. (Ethics reference number H0017462)

The lumbar erector spinae (LES) is a large muscle mass located lateral to the multifidus muscle and is covered by the erector spinae aponeurosis. The muscle mass is divided mainly into lateral (iliocostalis lumborum pars lumborum and iliocostalis lumborum pars thoracis) and medial (longissimus thoracis pars lumborum and longissimus lumborum pars lumborum) divisions by the erector spinae aponeurosis and an intramuscular aponeurosis [99]. In the lumbar region, the spinalis muscle has spindles that attach to the first two lumbar vertebrae, but it is irregular and poorly developed in this area [84].

The main actions of the thoracic and lumbar sections of the ES muscle are to extend the vertebral column, contribute to the movement of the lumbar spine via their pelvic attachments and control the rate of flexion against gravity [85, 86, 98, 100, 101]. The majority of muscles fibres in the ES muscles are slow twitch, fatigue resistant type I muscle fibres, making these muscles suited for one of its main actions of working tonically to maintain the upright posture [102]. Unilaterally the ES muscles are involved in lateral flexion of the trunk [73]. The LES muscles specifically, balance, stabilise and control shear forces on the lumbar spine during axial rotation movements [103]

1.2.4.2 The deep layer: The transversospinalis muscle group

The transversospinalis group consists of three muscles, the rotatores, semispinalis and multifidus muscles. The rotatores (Figure 1.7) and semispinalis muscles originate from the transverse processes of the vertebrae and insert into the spinous processes of the vertebrae above [73]. The rotatores muscle consists of cervicis, thoracis and lumborum segments, named depending on their superior attachment. They are small muscles spanning 1-2 vertebral segments and are thought to contribute minimally to momentum, but rather act as proprioceptive transducers providing feedback to influence the actions of surrounding muscles [98, 104]. The semispinalis muscle has the longest fascicles of this group of muscles and consists of capitis, cervicis and thoracis segments. They span 4-6 vertebral segments and are involved in the extension of the head and cervical and thoracic spine [73, 84]

Figure 1.7. The rotatores muscles

The image shows the rotatores and levatores muscles. The rotatores muscles are the deepest of the transversospinalis muscle group. (Ethics reference number H0017462)

The multifidus (MF) muscle (Figure 1.8) extends the length of the vertebral column and is formed by several triangular fleshy and tendinous fasciculi that are thickest in the lumbar region [73]. This muscle has traditionally been described as part of the transversospinalis group of muscles [73, 85]. In the lumbar spine however, studies have demonstrated that the MF muscle has a spino-transverse arrangement instead, with the muscle dividing into five bands (L1-L5) that are innervated segmentally [105, 106]. Each band arises from a tubercle at the tip of the spinous process, its lateral surface and the lamina. The bands further divide into several fascicles with a caudal insertion that varies from level to level, but the typical arrangement is fascicles arising from the lamina (deep fibres) insert into the mamillary process 2 vertebrae below. The fascicles from the lateral surface of the spinous process (intermediate fibres – absent at L5) insert 3 vertebrae below and the fascicles arising from the tubercle (superficial fibres) insert into the mamillary process 4-5 vertebrae below, the sacrum or the ilium [105, 106]. The lumbar multifidus muscle contributes to extension of the lumbar spine [107] and has a dual role as stabiliser of the spine, controlling intersegmental motion via its deep muscle fibres and generating trunk extension and control of spine orientation via its superficial fibres [105, 107-109].

Figure 1.8 The lumbar multifidus muscle

A

B

Image A: posterior longitudinal view of the muscles of the back. Labelled are the lumbar multifidus muscles, the erector spinae muscle and the gluteus maximus muscles. Image B: posterior lateral view of the same muscles. Note the increase in the size of the lumbar multifidus muscle from L2 to S1 spinal levels. (Ethics reference number H0017462)

1.2.4.2.2 Interspinales and intertransverserii and levatores costarum

The interspinales, intertransversii and levatores costarum muscles are part of the minor deep layer of muscles of the back [73]. The levatores costarum muscles elevate the ribs and assist in respiration. The interspinales and intertransversii muscles are small muscles that are located between the superior and inferior aspects of the spinous and transverse process of the spine, respectively. These muscles are not prime movers of the spine. Instead, they are rich in muscle spindles and are described as proprioceptive muscles for control of the position of the spine and its movements [84]

1.2.5 Other important muscles and anatomical structures of the trunk

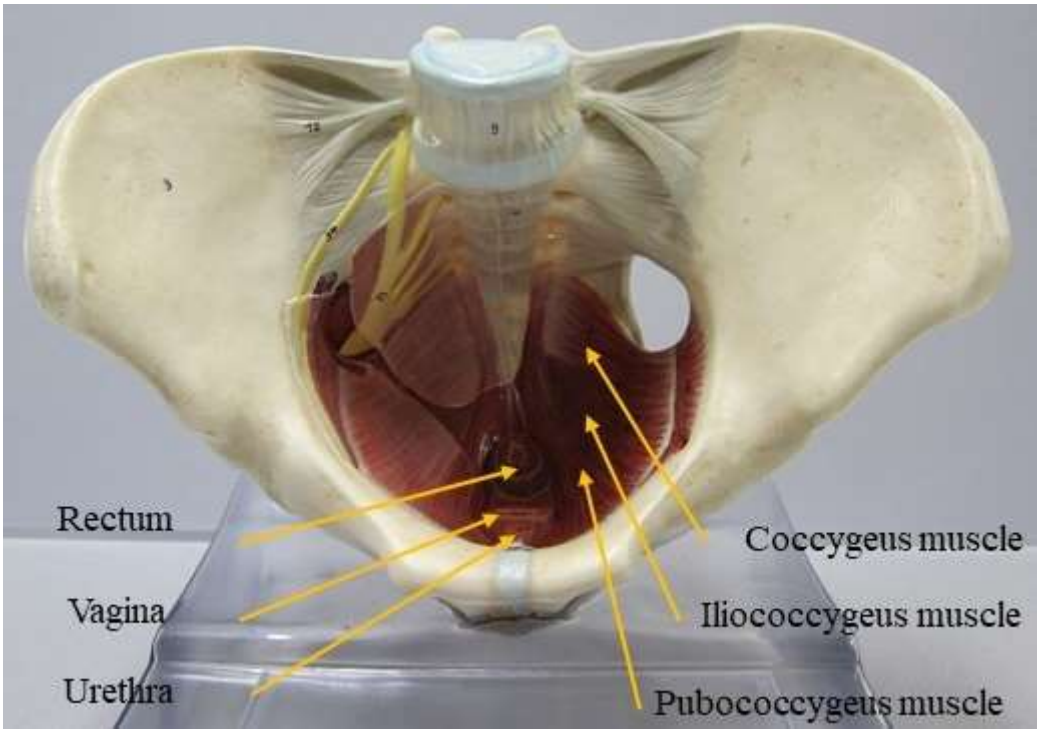
1.2.5.1 The iliacus and psoas major (iliopsoas) muscle

The Psoas major (Figure 1.5) is a long muscle that arises from the anterolateral surfaces of all lumbar vertebrae. It descends into the upper part of the anterior compartment of the thigh and inserts into the lesser trochanter of the femur together with the iliacus muscle to form the iliopsoas muscle [85, 86, 110, 111]. The iliopsoas muscle is primarily a hip flexor although ipsilateral lateral flexion of the trunk has also been described as one of its functions [85]. However, as the only muscle group in the body with direct attachment to the spine, pelvis and femur [112] iliopsoas can potentially generate compression forces which increase spinal stiffness [98, 113, 114] and control shear forces of the lumbar joints [101].

1.2.5.2 Diaphragm and pelvic floor (PF) muscles

The diaphragm and pelvic floor muscles are muscles of respiration and continence, respectively. However, they act together with the abdominal muscles to create and regulate intra-abdominal pressure and therefore they play an essential role in the function of the muscles of the trunk [75, 115]. The musculotendinous diaphragm seals the inferior thoracic aperture and serves as the roof of the abdominal muscular complex [104]. The pelvic diaphragm, the perineal membrane and the deep perineal pouch muscles form the pelvic floor. Increased intra-abdominal pressure is thought to be beneficial in all everyday activities by producing extensor torque and spinal unloading [76, 115].

Figure 1.9. The pelvic floor muscles



Model of the pelvis showing the pelvic floor muscles

1.2.5.3 The thoracolumbar fascia

The lumbosacral spine is essential for the postural stability of the human body, but on its own is unable to withstand the loads it is exposed to on a daily basis [116]. The thoracolumbar fascia (TLF) (Figure 1.10) is a myofascial and aponeurotic band that covers the posterior trunk, and is continuous with the paraspinal fascia of the sacral, lumbar, thoracic and cervical regions [116]. The TLF consists of three layers of fascia (anterior, middle and posterior) that envelop the deep muscles of the back and trunk, separating them into three components [85, 98]. The anterior layer of the TLF is thin and covers the anterior surface of quadratus lumborum. The middle layer lies behind quadratus lumborum and attaches medially to the tips of the lumbar transverse processes and intertransverse ligaments [85, 86, 98, 117]. The posterior layer is the thickest of the three layers and it divides into two laminae that cover the muscles of the back [91, 98, 118] and provide attachment for muscles of the shoulder girdle and anterolateral abdominal wall [91, 98, 104, 118]. The TLF is a retinacular belt for the muscles of the back [104] that aids extension forces in lifting [95, 113], plays a proprioceptive and nociceptive role in the back [116] and allows effective transfer of loads between the lower limb and upper limb.

Figure 1.10. The thoracolumbar fascia

Image of the thoracolumbar fascia and selected extrinsic muscles of the back. Labelled are the trapezius and latissimus dorsi muscles, which attach to the spine via the thoracolumbar fascia. (Ethics reference number H0017462)

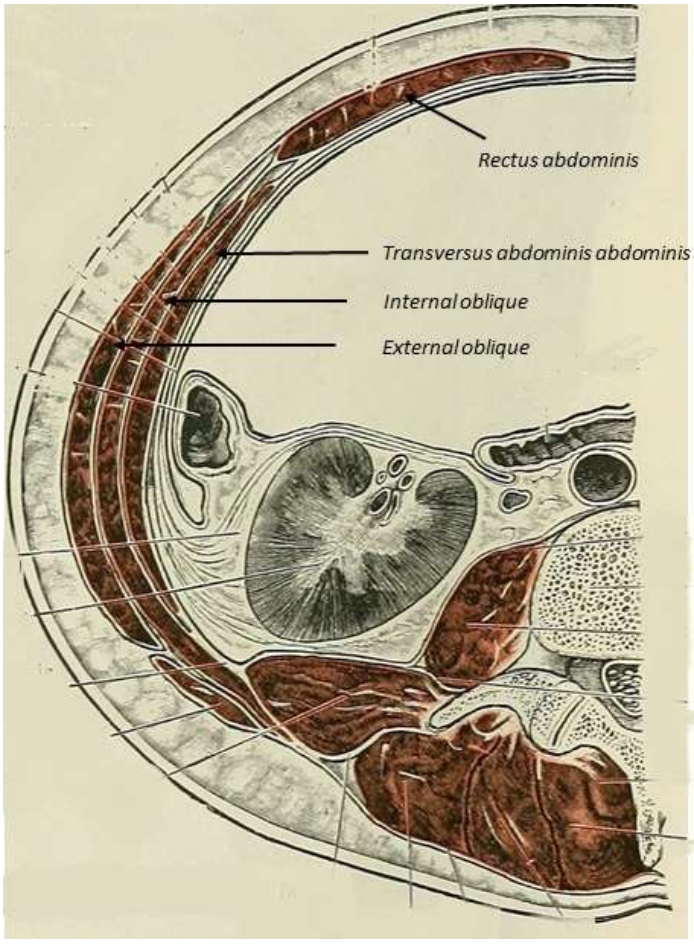
1.2.6 Cross-sectional anatomy of the muscles of the trunk

In this section the cross-sectional or axial anatomy of the muscles of the trunk at the lumbar spinal level will be described.

The rectus abdominis (RA) muscle (Figure 1.11) is a strap-like muscle located on the anterior aspect of the abdominal wall, lateral to the midline [84]. The medial border of the RA muscle is close to the linea alba, a tendinous raphe formed by the interlacing of the aponeuroses of the lateral abdominal muscles, that separates the right and left RA muscles in the midline [84]. The muscle is encased by the rectus sheath. Inferior to the arcuate line (horizontal line half way between the umbilicus and the pubic crest), the rectus sheath does not have contact with the transversalis fascia, as all three layers of aponeuroses, from EO, IO and TrA, pass anterior to the rectus abdominis. Superior to the arcuate line, the posterior lamina of the rectus sheath is in contact with the transversalis fascia [84, 119]. The lateral abdominal muscles are from superficial to deep, the external oblique, internal oblique and transversus abdominis muscles respectively. Anteriorly, the aponeuroses of the lateral abdominal muscles blend to form the rectus sheath on

the lateral border of the RA muscle. The aponeurosis of the IO muscle splits to contribute to the anterior and posterior layers of the rectus sheath above the arcuate line. The aponeurosis of the EO blends with the anterior layer, while the aponeurosis of the TrA muscle blends with the posterior layer of the sheath [84, 120]. The size of the abdominal muscles is correlated with BMI, and the descending order of thickness for these muscles has been reported to be RA the thickest, followed by IO, EO and TrA muscle the thinnest [121].

Figure 1.11 Cross-sectional image of right trunk muscles (approximately L2-3 spinal level)

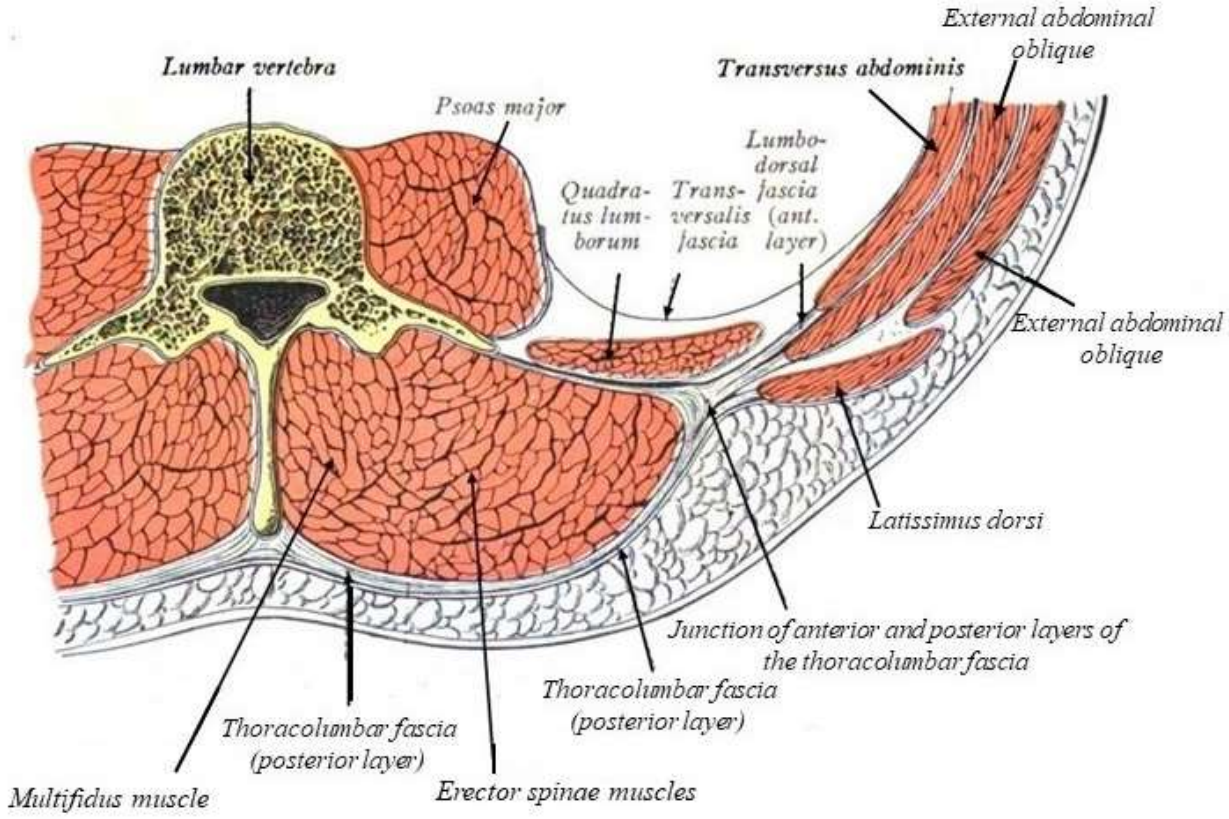


Interactive archive book. Image from page 326, Sobotta's Atlas and text-book of human anatomy, 1914. Modified by William Cuellar

Posteriorly (Figure 1.12) the multifidus muscle is the most medial of the large back muscles and extends from the tip of the spinous process and along its lateral surface to the vertebral lamina, filling the space between spinous and transverse processes [101]. The muscle covers the area of

the lamina, from its medial aspect to the mamillary process [105]. The posterior fascicles of the MF muscle attach to the posterior layer of the TFL [105], and the lateral border is at the intermuscular fascia with the longissimus muscle [122]. The size and shape of the MF muscle changes from L1 to L5, being slightly more round and smaller at the upper spinal levels and larger and broader in the lower ones [122]. The difference in size of the MF muscle from L1 to L5 relates to its anatomical arrangement which, in the lumbar spine, is comprised of 5 bands, each one arising from the tip of the spinous process, its lateral surface and the lamina and further subdividing into fascicles with caudal insertions that vary at each level [105, 106]. At L5 the MF muscle has components from all 5 bands, accounting for its larger size compared with the upper levels.

Figure 1.12 Cross-section of the lumbar paraspinal muscles (approximately L3-L4 spinal level)



Wikimedia commons, Sobotta's Atlas and text-book of human anatomy, 1909. Modified by William Cuellar

As described previously, the LES muscle is comprised of two separate muscles, the longissimus muscle medially and the iliocostalis muscle laterally [100]. The medial border of the LES muscle mass is the intermuscular fascia with the multifidus muscle. Anteriorly, it extends from the mamillary process along the transverse process of the vertebra and continues laterally to the lateral raphe, a complex of dense connective tissue formed by the aponeuroses of the latissimus dorsi, TrA and IO muscles, and the middle and posterior layers of the TLF [99]. The middle layer of the TFL covers the anterior aspect of the LES [84, 116]. Posteriorly, the ES muscle is covered by the posterior layer of the TFL. Like the MF muscle, the LES muscle becomes progressively larger from the upper to the lower spinal segments due to an increase in the muscle belly size [99].

The quadratus lumborum (QL) muscle is a flat, irregularly shaped muscle that is broader in the lower segments [84]. It is located anterior to the LES muscle and attaches medially to the apices of the transverse lumbar vertebrae via small tendons [84] and laterally to the aponeurosis of the deep lateral abdominal muscles. The investing fascia of the QL muscle is covered anteriorly by the anterior layer of the TFL and posteriorly by the middle layer of the TFL [84, 116]. The psoas muscle is a large muscle that covers the area lateral to the vertebral body and anterior aspect of the transverse process [84]. Anteriorly, it is covered by a thin layer of fascia that is an extension of the abdominal transversalis fascia [116].

The three lateral abdominal muscles are also visible in the posterior aspect of the cross-sectional area of the lumbar region (Figure 1.7). The aponeuroses of the TrA and IO muscles blend with the middle layer of the TFL at the lateral raphe, which in turn provides indirect attachment to the vertebra [116].

1.2.7 Function of the muscles of the trunk

Muscles of the trunk are essential for an individual's ability to perform fundamental functional activities of daily living due to the complex role they play in load transfer, force dissipation, control of balance and posture, and trunk and pelvic movement [6, 8, 9]. Normal trunk movement in everyday activities requires the spinal stabilization system to constantly maintain co-contraction and fine coordination between the different muscular systems [76, 77, 123-127]. The RA, TrA, ES and MF muscles along with the psoas, gluteal and hamstring muscles provide trunk flexion and extension movements in the sagittal plane, while the IO, EO and QL muscles are involved in lateral flexion and trunk rotation movements [84]. Co-contraction of these muscles in conjunction with the pelvic floor muscles and the diaphragm increase intra-abdominal pressure [74-77, 88, 113, 128, 129] and the TLF's longitudinal tension [95, 113], thus facilitating the transmission of

forces from the upper to the lower limbs for everyday tasks.

The ES muscle has a large proportion of type I fibres [102] and activates asymmetrically/contralaterally in one-sided tasks and symmetrically in two-handed tasks [130], making this muscles suited to extend the spine from the trunk to the pelvis, produce movement of the hip and increase trunk stiffness to withstand external, destabilising forces involved in everyday functional tasks [87]. The MF muscle in particular, transfers loads through the lower spine and has a dual role as stabiliser of the spine, controlling intersegmental motion via its deep muscle fibres, and generating trunk extension and control of spine orientation via its superficial fibres [105, 107-109]. The MF and IO muscles maintain constant activation during most everyday activities and symmetrical co-contraction during lifting tasks, therefore providing tonic dynamic control of the lumbar spine and pelvis [130, 131]. The MF and TrA muscles play a major role in preparing the trunk to counteract the effect of gravity, postural changes and destabilizing forces caused by movements of the limbs and body, by tonically activating at low levels during most activities of daily life [76, 77, 132-135]. The mechanism responsible for the anticipatory, stabilising responses of the muscles of the trunk are proprioceptive transducers located in the passive musculoskeletal system (vertebrae, facet joints, intervertebral discs, spinal ligaments and joint capsules) and the minor deep muscles of the back [80, 123, 124, 136]. Decreased trunk proprioception [10] and muscle imbalance common in the presence of pathology [78] have the potential to alter posture and balance, increasing the risk of falls due to loss of functional or dynamic stability [137]. Physical activity plays an important role in maintaining the size and quality of the abdominal and MF muscle of older adults [138]. Age-related decreases in physical activity have the potential to affect these muscles through changes in the biochemical composition of muscle fibres and the loss of muscle mass due to the removal of the trophic stimulus of the activity leading to sarcopenia [20]. Associations between abdominal and MF muscles and measures of physical activity will be examined in Chapter 7 of this thesis.

1.2.8 Age-related changes in skeletal muscle, including muscles of the trunk

With increasing age, skeletal muscle undergoes changes to its morphology, function, fibre type and quantity, innervation and composition [139]. Many of these changes are modest and occur progressively until the age of 50 years, but then become more pronounced after the age of 60 years [139]. Upper and lower limb skeletal muscle mass peaks in early adulthood [11, 19] and gradually declines by 30% between the ages of 20 and 80 years [48]. Abdominal muscle size decreases between 23-48% in older women living independently when compared with younger

controls [138]. Age-related declines in skeletal muscle size match closely declines in muscle strength, especially after the age of 60 years. It is thought that decreases in skeletal muscle size occur as a consequence of decreases in the number of muscle fibres, and although this decline occurs equally for type I (slow twitch, fatigue resistant) and type II (fast twitch, responsible for muscle power) fibres, there is a greater decrease in the size of type II muscle fibres with increasing age [138].

Along with decreases in muscle fibres, the two key elements contributing to the age-related decreases in muscle mass and strength are reductions in the number of functioning motor units and a decrease in muscular endurance, or the ability to resist muscular fatigue [45, 139]. As the number of functioning motor neurones decrease with ageing, the remaining motor units increase in size, so that every remaining motor neuron innervates a greater number of muscle fibres, which has been explained as an age-related process of denervation of muscle [139]. Age-related denervation of skeletal muscle is associated with loss of motor units and loss of muscle fibres, contributing to declines in strength and power and increases in muscle wasting, including muscle of the trunk in older adults [45, 139]. An age-related decrease in muscular endurance, or the decrease ability to resist muscular fatigue is thought to be linked to a decrease in neural drive [139]. In the case of the lower limbs and muscles of the trunk, this is reflected in a decline in the ability to activate muscles to adjust posture and centre of gravity following external disturbances, increasing the risk of falls [138-143]. The decline in type II fibres, a decrease in functioning motor units, an increase in muscular fatigue and a decrease in mechanical stimuli due to decreased physical activity, may help to explain the progressive difficulties older adults experience performing daily activities and the increase in falls after the age of 60 years.

Another of the significant age-related changes in skeletal muscle are increases in intramuscular fat infiltrations and connective tissue, resulting in decreases in contractile muscle mass [65]. The obvious consequence of increases in noncontractile tissue in skeletal muscle is the increased cost of carrying inert mass during daily activities. Increased intramuscular fat infiltrations also have the consequence of increased macrophages that mediate the release of pro-inflammatory cytokines/chemokines (TNF-a, IL-6, IL-1) and adipokines (leptin, adiponectin and resistin) that have the potential to have detrimental effects on skeletal muscle (age-related anorexia) [139] and insulin sensitivity [144]. Increased intramuscular fat infiltrations in paraspinal muscles is associated with reduced functional capacity, increased risk of falls and self-reported measures of physical function [145, 146].

1.2.9 The role of trunk muscles in walking

Walking requires a disturbance of the trunk's balance which is sustained by the tonic action of the muscles of the trunk and pelvis while standing at rest [89]. During walking, the pelvis experiences translational and rotational movements in different planes, and forces from the ground are transmitted to the lower limb and trunk, requiring a kinetic chain of actions by the muscles of the trunk that is far more complex than that at rest [89]. Electromyography studies have described the electrical activity of muscles of the trunk during the gait cycle, reporting that the electrical activity of the erector spinae muscle group starts before heel strike, with maximal activation at heel strike (approximately 50% of the gait cycle) and then continuing to be active through the pre-swing phase [89, 132]. The electrical activity of the MF muscle spans from the 12% - 90% of the gait cycle, being more active during heel strike. This electrical activity pattern is similar for the quadratus lumborum muscle [89, 132]. The RA, EO and IO muscles show continuous electrical activity during the gait cycle [89, 147], with EO and IO sometime displaying intermittent activity towards the end of the gait cycle [89, 147]. Increases in walking speed increase the electrical activity and the percentage of activation during the gait cycle of the abdominal and ES muscles, with these muscles displaying a more phasic electrical activity to provide stability of the trunk [89, 147].

Gait pattern and activity of the trunk muscles and lower limb change with increasing age, that in turn, increases the risk and fear of falling in older adults [148]. Older adults tend to walk slower, with shorter stride length, reduced co-activation of muscles of the trunk and reduced range of motion of the spine, trunk and lower limbs [149]. Crawford et al. [149] reported that with increased walking speed, there was an increase in duration of activation in the deep MF, abdominal and ES muscles in older adults that was related to the increased work demand to maintain upright posture. However there was a decrease in activation of the superficial MF muscle along with decrease spine and trunk movement [149], which may help to explain the decrease in lumbar lordosis and kyphotic postures commonly seen in older adults [150]. The changes in activation seen in the trunk muscles of older adults, have the potential to guide clinicians to design tailored exercise programs that have a walking component designed to increase activation of the muscles of the trunk.

1.2.10 Muscles of the trunk and measures of physical function

Functional autonomy depends on the complex interaction of four main dimensions, namely,

physical, social, emotional and cognitive function [151]. Physical capacity or physical function refers to an individual's ability to make normal use of his/her sensory-motor capabilities to undertake activities of daily living such as walking, climbing stairs or standing from a sitting position [151, 152]. There are many scales and tests that have been developed to assess a person's physical function such as the short physical performance battery and the timed up and go tests. However, these tests are mainly designed to test lower limb function. There are few studies addressing whether size, activation or muscle quality of the trunk muscles are associated with measures of physical function in older adults [138]. The few studies investigating these associations have found that increased intramuscular fat infiltrations in paraspinal muscles is associated with reduced functional function, increased risk of falls and low scores in self-reported measures of physical function, as well and being a predictor of poorer long-term physical function outcomes for older adults with low back pain [145, 146]. The paucity of information on the effect of age-related changes in muscles of the trunk on physical function will be addressed in Chapter 3.

1.2.6 Assessment muscles of the trunk in clinical practice

Clinical approaches to assessing muscles of the trunk include measures of strength (e.g. isokinetic and isometric endurance muscle testing, dynamometry and clinical muscle testing [153]), measures of activation and fatigue (e.g. electromyography) and measures of morphology (e.g. ultrasound imaging). Standardised assessment tools that measure different aspects of trunk muscle morphology, function and performance are fundamental for clinical practice and research. Isokinetic and isometric endurance muscle testing, dynamometry and clinical muscle testing have been used extensively in clinical and research settings [153]. As decreased muscle size and dysfunction with ageing are key features in sarcopenia, and there is a paucity of information on the effects these age-related changes have on the physical function (addressed in Chapter 3) of older adults, this thesis will focus on the morphology of invididual muscles to ascertain their individual and global contribution to normal function of older adults. Therefore, only modalities that allow assessment of individual muscles, i.e., electromyography and imaging, will be discussed in this section.

Surface and intramuscular electromyography (EMG), an electrodiagnostic tools used to assess electrical activity in muscle, have been used to sense isometric muscle activity, refractory periods and calculate muscle activation patterns and joint compression forces, among others [123, 124, 154-156]. However, there are several limitations to this technique, particularly with the use of

intramuscular fine needle wires, because it is costly, uncomfortable and carries the risk of infection [157], which makes it difficult to use this particular technique outside research settings. Also, there does not seem to be an exact relationship between EMG signals and muscle force for either invasive or non-invasive EMG approaches [158, 159].

Computed tomography (CT) and magnetic resonance imaging (MRI) have been used to assess trunk muscle thickness, cross-sectional area (CSA) and muscular moment arm (the shortest perpendicular distance from the line of force to the axis) for use in biomechanical studies [160, 161]. MRI has been described as the "gold standard" measure for assessment of trunk muscles, because MRI images have excellent soft tissue contrast that enables clear demonstration of anatomy and allows accurate confirmation of spinal levels as well as making it possible to assess large muscles and multiple muscles at the same time [114, 162-164]. CT scanning can also be used to measure muscle composition by measuring muscle attenuation (MA), a radiological characteristic that quantifies the macroscopic accumulation of intramuscular fat, with a higher attenuation score indicating less intramuscular fat accumulation [138, 165]. Increased fat infiltrations in skeletal muscle have been reported to be an indicator of poor muscle quality, and to be associated with decreased muscle strength [166, 167] and increased risk of hospitalization in older adults [168]. Both CT and MRI are expensive and not always readily accessible making it difficult to use these techniques in clinical settings or research studies. Also, CT exposes patients and research participants to ionising radiation.

Real-time ultrasound imaging (USI) has been used to measure trunk muscle thickness, changes in muscle length, muscle timing and activation, CSA and to identify atrophy [122, 169-173]. USI has also been used in clinical settings for the re-education of muscles [174], and visual biofeedback in rehabilitation [122, 175]. USI has been increasingly used for the assessment of trunk muscles both for research and in clinical settings because it is safe, non-invasive, portable, patients are not exposed to ionising radiation and is relatively inexpensive [157, 176]. However, some limitations of this technique include its limited field of view that makes it unsuitable for imaging large muscles [162].

1.2.7 Validity and reliability of EMG and imaging techniques used to measure muscles of the trunk of older adults

Establishing the reliability of measurements is essential to interpret outcomes and make clinical decisions based on research findings [177]. Reliability has been defined as the extent to which

measurements can be consistently replicated [178, 179], while validity concerns whether the instrument used is accurate and it measures what it intends to measure [178].

The trunk muscles investigated in this thesis included the RA, TrA, IO, EO muscles and the MF muscles. Studies in younger people have demonstrated the validity and reliability of a range of methods for measuring abdominal and MF muscles in this age group. Reliability measures of peak moment and normalised EMG values during submaximal contractions of MF and abdominal muscles have been reported to have good reliability (dependability coefficient 0.65 - 0.88) [180]. CT and MRI-based studies have reported high reliability (Intraclass Correlation Coefficient ICC>0.75) for measures of abdominal and MF muscle size and attenuation [145, 181-184]. The validity of USI has been examined in young adults; if strict protocols were followed, USI was as accurate as MRI in determining the size of MF [162]. Reliability of measurement of abdominal and MF muscles using USI have been reported to be moderate to substantial (ICC=0.75-1.00) [177].

The validity and reliability of methods established in younger people may not be similarly observed in older people for several reasons, including features of aging such as spinal degeneration, decreased water content in skeletal muscle and increased fat infiltrations and fibrous tissue content of skeletal muscle, which increase the difficulty of assessing ageing muscles [122, 185]. Therefore, a comprehensive understanding of the performance of these methods in older people is important. The systematic review and narrative update in Chapter 3 addresses this gap in the literature by describing the validity and reliability of these measures in older adults. The study in Chapter 5 addresses the gap in test-retest reliability measures of abdominal and MF muscles using USI, identified in the systematic review in Chapter 3.

1.2.8 Concluding Comments

This section described the trunk muscles, particularly the abdominal and MF muscles, as postural muscles tonically active during daily upright activities and essential to perform fundamental functional activities of daily living due to the complex role they play in load transfer, force dissipation, control of balance and posture, and pelvic movement [6, 8, 9, 77, 86, 132, 147, 186]. It also discussed the actions of these muscles, their involvement in physical function, and the validity and reliability of measurements of abdominal and MF muscles using various EMG and imaging modalities. The systematic review in Chapter 3 addresses the paucity in information regarding the validity and reliability of measures of trunk muscles using EMG and imaging techniques by providing a synthesis of the literature on measures of validity and reliability of trunk muscles

using various imaging modalities and associations between trunk muscles and physical function of older adults

In the next section, vitamin D will be discussed including production, prevalence of deficiency, aetiology and its role in skeletal muscle morphology, strength and physical function in older adults.

1.3 VITAMIN D

In Section 1.1, sarcopenia was described as an age-related process characterised by a generalised decrease in lean muscle mass, peripheral muscle size and the consequent loss of muscle strength and muscle function [16-18]. In section 1.2, the essential role of muscles of the trunk was described, as well as the current gaps in knowledge. In this section, vitamin D and its effect on skeletal muscle will be discussed. Vitamin D deficiency is common in community-dwelling and institutionalised older adults and has the potential to impact on skeletal muscle, contributing to sarcopenia and affecting physical function [187].

1.3.1 Introduction

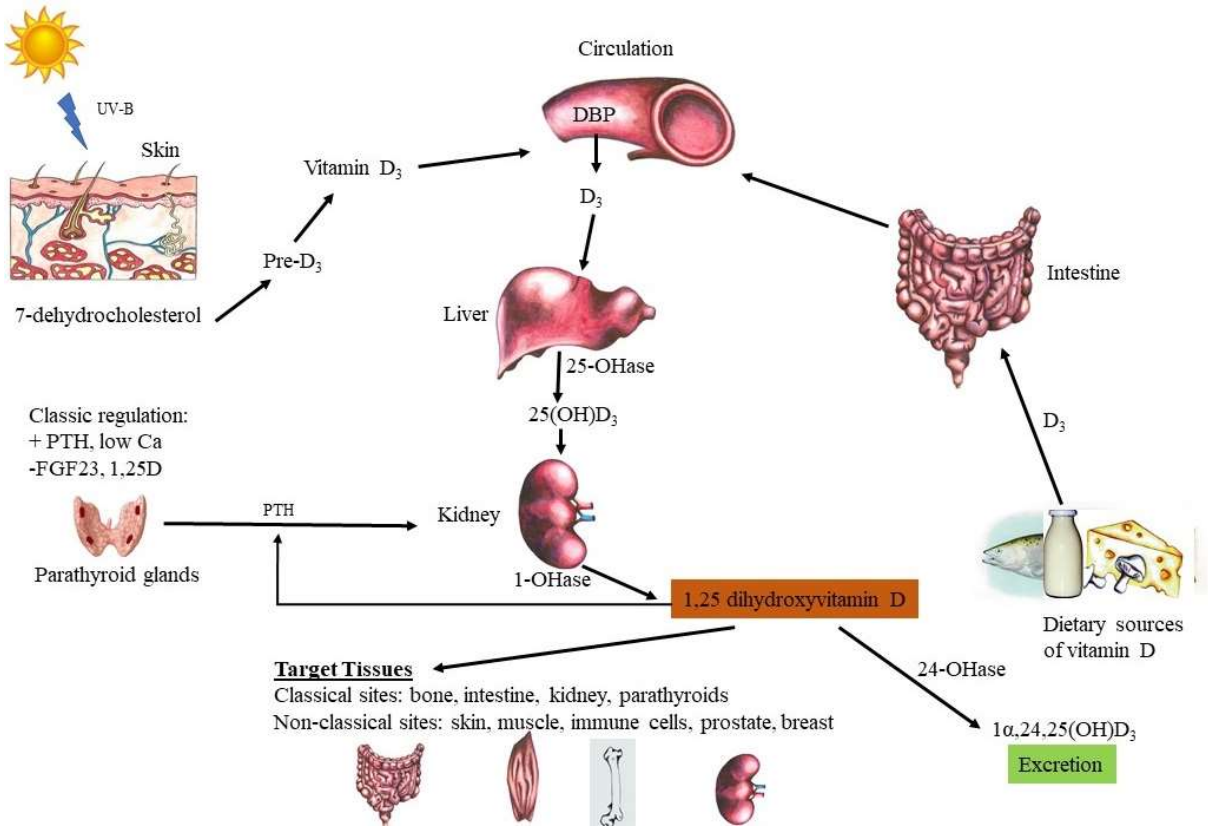
Population levels of serum vitamin D are variable around the world, but deficiency is common in older adults due to decreased production of vitamin D in the skin, insufficient dietary intake and decreased sun exposure due to decreased physical activity, mobility or institutionalisation [188-191]. This section will discuss vitamin D production, classification, prevalence and symptoms of vitamin D deficiency. The effects of vitamin D deficiency and supplementation on skeletal muscle size, mass and strength, and associations with measures of physical function will also be discussed.

1.3.2 Vitamin D Production

The molecules known as vitamin D are, in fact, not vitamins, but steroid hormones. Their active form (1,25-dihydroxyvitamin D) is primarily involved in the regulation of plasma calcium and phosphate levels which are essential for mineralisation of bone and the normal functioning of the nervous and muscular systems and hormonal secretion [192, 193]. Humans obtain vitamin D by exposure to sunlight (Figure 1.12), from diet and supplements. Very few foods naturally contain vitamin D therefore in general food has a minor contribution to vitamin D levels [192]. When the

skin is exposed to ultraviolet B radiation, naturally occurring 7-dehydrocholesterol in the skin is converted to pre-vitamin D_3, which is immediately converted to vitamin D_3 (Cholecalciferol). Any excess pre-vitamin D_3 or vitamin D_3 produced in the skin is destroyed by sunlight, thus preventing vitamin D intoxication [192]. Over-the-counter supplements available are made by ultraviolet irradiation of ergosterol from yeast (D_2 or ergocalciferol) or ultraviolet irradiation of 7-dehydrocholesterol contained in lanolin (D_3).

Figure 1.13 Vitamin D cycle



Vitamin D cycle. Drawings: Rhiannon Arnold. Sources [192, 194-196]

Vitamin D (D_2 or D_3) synthesised in the skin or acquired through diet is stored in fat cells and later released and circulated to the liver where it undergoes hydroxylation and converted to the still biologically inactive form 25-hydroxyvitamin D (25(OH)D or Calcidiol) [192]. 25-hydroxyvitamin D is the most abundant circulating form of vitamin D and is used to assess vitamin D status. 25-hydroxyvitamin D undergoes further hydroxylation in the kidneys where it is converted to the biologically active form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$ or calcitriol) [192]. The most critical role of 1,25-dihydroxyvitamin D is the tight regulation of extracellular

calcium and phosphate within the required limits to maintain homeostasis which is essential for the normal function of nerve and muscle [197].

Vitamin D production is dependent on age, body mass index, sun exposure, time of day, latitude, the season of the year, geographical location and skin pigmentation. Serum 25(OH)D levels are lower in winter than summer as less vitamin D is synthesised in winter, especially in those who have dark skin, the elderly and those who dress with decreased potential for skin exposure to sunlight for cultural reasons or for sun protection [60, 198-200]. Although older adults can photosynthesize pre-vitamin D_3, ageing itself can substantially decrease the capacity to produce pre-vitamin D3 in the epidermis and dermis [58, 190, 201]. Obese individuals produce about half the amount of vitamin D compared to non-obese individuals after sunlight exposure [60].

1.3.3 Classification of vitamin D status

The vitamin D status of an individual can be classified into vitamin D adequacy, mild deficiency, moderate deficiency and severe deficiency according to their serum 25(OH)D level (table 1.2). Vitamin D adequacy is defined as serum 25-OHD concentration above 50 nmol/L. In the state of adequacy, vitamin D has no adverse effect on skeletal homeostasis and 50 nmol/L is considered the minimum target level for adequate bone health, mineral homeostasis and muscle function [191, 193, 200].

Table 1.2 Classification of vitamin D status [200]

Vitamin D status	Serum 25-OHD levels
Vitamin D adequacy	≥ 50 nmol/L
Vitamin D mild deficiency	30 - 49 nmol/L
Vitamin D moderate deficiency	12.5 - 29 nmol/L
Vitamin D severe deficiency	< 12.5 nmol/L

1.3.4 Vitamin D deficiency - prevalence

Population levels of serum vitamin D are variable, but deficiency is highly prevalent all over the world, particularly in Asia and the Middle East. In Australia, approximately 31% of adults have serum 25-hydroxyvitamin D below the minimum 50 nmol/L and it may be as high as 50% for

women living in the southern states during the winter months [200]. The most common groups at risk of vitamin D deficiency include young children, pregnant women and older adults [191]. Vitamin D deficiency is common in older adults with reports of 30-90% of older aged adults recording deficiency [188-191, 198, 202-205]. In Australia, the groups of people most at risk of developing vitamin D deficiency include the elderly, people in residential care, dark-skinned people and people who have limited sun exposure (Table 1.3). Some reports estimate the number of people with vitamin D deficiency or insufficiency to be 1 billion worldwide [192, 205, 206]. Low vitamin D levels have been described as endemic in North America, Europe, the Middle East, Africa and South Asia [55, 199, 204, 207, 208]. In the United States (US), the prevalence of vitamin D deficiency has been reported to be 10 times higher in African-American than Caucasian older women [204].

Table 1.3 Adult groups at high risk of vitamin D deficiency [200]

a) Older or disabled people in low-high level residential care
b) Dark-skinned people of either sex
c) People with a disability or chronic disease
d) Fair-skinned people who avoid skin exposure
e) Obese people
f) People working in enclosed environments

1.3.5 Vitamin D deficiency symptoms in older adults

The common clinical symptoms of vitamin D deficiency in the elderly include symmetrical proximal muscle weakness, particularly in the lower limbs, associated with a feeling of heaviness in the legs, easy fatigability, increased medio-lateral body sway, hyperreflexia and difficulty climbing stairs or rising from a chair [53-61].

Mild vitamin D deficiency leads to hyperparathyroidism and high bone turn over [198]. Moderate vitamin D deficiency has been associated with decreased bone density, increased bone turn over and the risk of hip fracture in older adults [198]. Finally, severe vitamin D deficiency has a significant effect on calcium homeostasis, bone mineralisation and skeletal muscle metabolism, resulting in osteomalacia in adults [198, 200]. Patients with severe deficiency can present with bone and muscle pains, weakness and pseudofractures [58, 192, 198, 200].

1.3.6 Vitamin D and its role in skeletal muscle size, mass and strength

Vitamin D plays a vital physiological role in normal skeletal muscle function, muscle development and growth [59, 209]. The mechanism is thought to be through $1,25(OH)_2D$ binding to a specific vitamin D receptor found in skeletal muscle [54, 210] leading to de novo protein synthesis and thus muscle cell proliferation and growth [59, 211]. Vitamin D regulates muscle phosphate and calcium transport across sarcolemma membranes. It influences intracellular calcium levels in the muscle cell and contributes to the general calcium homeostasis in the body [61, 212-215]. The main functions of vitamin D on muscle are listed in table 1.4

Table 1.4 Main functions of vitamin D on muscle [60]

a) Increases amino acid uptake in muscles
b) Alters phospholipid metabolism in muscles
c) Vitamin D deficiency causes myopathy
d) Nongenomic effects on muscles
e) Increases troponin C in muscles

A systematic review and meta-analysis of 17 RCTs examining the effect of vitamin D supplementation on muscle strength revealed that vitamin supplementation had no significant effect on grip strength (8 studies, standard mean difference (SMD) -0.02), proximal trunk muscle strength (latissimus dorsi, trapezius, rhomboid muscles) (1 study, SMD -0.23) or lower limb strength (8 studies, SMD 0.01). However, 4 studies reported positive effects of vitamin D supplementation on grip strength and lower limb strength in participants with baseline 25(OH)D ≤ 25 nmol/L [206]. A more recent systematic review and meta-analysis of 30 RCTs examined the effect of vitamin D supplementation on peripheral muscle strength, mass and power [216]. There was great variation in the vitamin D supplementation doses in the studies included in this review (300 – 8600 IU/day). Pooled results from 19 studies (2349 people) revealed a small but statistically significant positive effect of vitamin D supplementation on lower limb muscle strength (SMD 0.19). Participants with 259(OH)D was ≤30 nmol/L obtained greater benefit than those with 25(OH)D ≥30 nmol/L (p=0.02). However, the pooled results from studies investigating the effect of vitamin D supplementation on grip strength (16 studies), muscle mass (6 studies) and power (5 studies) showed no statistically significant effect of vitamin D supplementation on these measures [216]. The evidence from these systematic reviews on the effect of vitamin D supplementation on upper and lower limb muscles seems conflicting. Nevertheless, in both cases, subjects with baseline serum 25(OH)D ≤30 nmol/L obtained greater

and positive effect of vitamin D supplementation on peripheral muscle strength. It is important to note that there were no studies investigating the effect of vitamin D supplementation on muscles of the trunk, more specifically, muscles that are prime torque producers such as the abdominal, erector spinae or MF muscles, included in these systematic reviews. Although the muscles assessed by Stockton et al. [206] are located in the trunk region, they are anatomically considered muscles of the upper limb as they received innervation from the anterior rami of cervical nerves and providing attachment of the shoulder girdle to the back and movement the upper limb are their primary functional roles. Therefore, studies investigating the effect of vitamin D on the size, mass, quality and strength of muscles of the trunk are needed (this will be examined in Chapter 6).

1.3.7 Vitamin D and its role in physical function

In a systematic review and meta-analysis, Muir et al. [217] reviewed 13 studies investigating the effect of vitamin D supplementation on gait, balance and quadriceps muscle and grip strength in older adults (60 years of age and older). In these studies, the baseline serum 25(OH)D ranged from 24.46 to 65.7 nmol/L, and supplementation doses ranged from 400 to 3000 IU/day. The SMD from these studies comprising 207 participants was -0.20 (95% CI = -0.39 to -0.01, P = .04), indicating a decrease in postural sway. Increased postural sway has been shown to be positively associated with balance and risk of falling [62]. Studies in which the participants were given doses of 800 to 1000 IU per day reported beneficial effects on lower limb muscle strength (SMD=0.05, 95% CI = -0.11 to 0.20). Three studies comprising 274 participants, reported improvements in time to complete the timed up and go test (TUG). The TUG test is a reliable and valid test that has been found to be positively associated with balance and functional mobility [218, 219]. No statistically significant effect of vitamin D supplementation on gait was found [217].

1.3.8 Concluding Comments

The literature reviewed in this section described the different classifications of vitamin D status, the prevalence of vitamin D deficiency and the effect of vitamin D supplementation on muscle size, muscle strength and functional capacity. The evidence from RCTs indicate that although vitamin D supplementation does not have a positive effect on upper or lower limb muscle strength, mass or power in subjects with serum 25(OH)D ≥30 nmol/L, there is a small, but significant positive effect on these muscles in subjects with 25(OH)D ≥30 nmol/L at baseline,

especially those who are older or in care institutions. The potential effects of vitamin D deficiency on muscles of the trunk and the effect of vitamin D supplementation on the size, strength or quality of these muscles have not been examined.

1.4 Summary

Sarcopenia is an age-related process characterised by a generalised decrease in lean muscle mass, peripheral muscle size and the consequent loss of muscle strength and muscle function (13-15). There is some evidence that ageing has a detrimental effect on muscles of the upper and lower limbs. However, the effect of ageing on muscles of the trunk is not fully understood. Although it would be reasonable to assume that the age-related changes described in peripheral muscle mass and strength for upper and lower limbs would be present in the muscles of the trunk, the potential effects these changes have in physical activity, physical function, quality of life and healthy ageing have not been established and should be investigated.

The reliability of EMG and imaging measures of the abdominal and MF muscles in older adults is not well established. The reliability of measurements of abdominal and MF muscles is essential to interpret outcomes and make clinical decisions based on research findings [177]. Finally, evidence from RCTs indicate that vitamin D supplementation may have a significant positive effect on muscles of the upper or lower limbs in subjects with 25-OHD ≥30 nmol/L at baseline, especially those who are older or in care institutions. However, the potential effects of vitamin D on muscle of the trunk have not been examined. The gaps in knowledge outlined in this chapter have directly informed the research questions of this work and will be discussed in the following chapter.

CHAPTER 2 – RESEARCH QUESTIONS

2.1 Research question 1

Upper and lower limb muscles decrease in size, isokinetic strength and percentage of type I fibres with increasing age [48]. These changes have been shown to be associated with decreases in physical function and quality of life of older adults [12, 152, 220]. However, there is little information regarding the changes in size that muscles of the trunk undergo with age and the effect these changes may have on the physical functioning of older adults. Research question 1 investigates the evidence for changes in function, composition and morphology of the muscles of the trunk and the effects of any changes on the physical function of older adults. It also investigates the evidence for the validity and reliability of measures of individual trunk muscle using EMG or imaging.

2.1.1 What evidence is there for changes in mass, strength, power, muscle composition/fat infiltrations and size and shape of the abdominal and MF muscles and the effects of any changes on the physical function of older adults?

2.1.2 What is the validity and reliability of measurements of abdominal and MF muscles among older adults.

A systematic review will be conducted to:

a. Provide a summary of the evidence for changes in function, composition and morphology of the abdominal and multifidus in adults aged 50 years and older.
b. Provide a summary of the evidence for the effect any composition or morphology changes in the abdominal and multifidus have on the physical function of adults aged 50 years or older.
c. Document the validity and reliability of electromyographic and imaging measurements of abdominal and multifidus muscles among adults aged 50 years and older.

Research questions 2 – 4 are defined in a volunteer sample of people that were part of The Vitamin D Effect on Osteoarthritis (VIDEO) study. The VIDEO study was a randomised, placebo-controlled and double-blind clinical trial conducted between June 2010 and December 2013 [221]. Participants were people aged 50-79 years, with symptoms of knee OA for at least six months with pain levels between 20-80 mm on a 100 mm visual analogue scale, and serum 25(OH)D levels between 12.5 and 60 nmol/L. Exclusion criteria included: severe knee pain or OA, conditions affecting oral drug absorption and surgery.

2.2 Research questions 2

The reliability of measurements of abdominal and MF muscles is essential to interpret outcomes and make clinical decisions based on research findings [177].

2.2.1 What is the test-retest reliability of ultrasound imaging for assessing abdominal and MF muscle thickness and MF CSA at the L2 - L5 vertebral levels in people aged 50-79 years with symptoms of knee osteoarthritis.

2.3 Research questions 3

Although there is RCT evidence that indicate that vitamin D supplementation may have a significant positive effect on muscles of the upper or lower limbs, the potential effects of vitamin D on muscle of the trunk have not been examined.

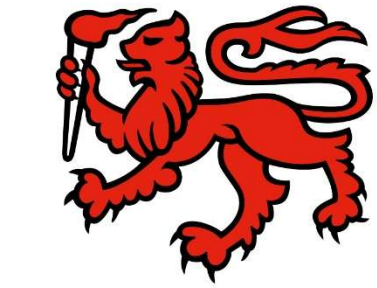
2.3.1 What is the effect of 12 months of vitamin D supplementation compared with placebo, on morphology and function of the abdominal and MF muscles of adults aged 50 to 79 years with low serum 25(OH)D levels.

2.4 Research questions 4

Age-related changes in muscles of the upper and lower limbs are well documented, as well as the effect of these changes on physical function. However, there is limited information regarding age-related changes in the abdominal and multifidus muscles and the potential effect these changes have on physical activity, physical function and quality of life.

2.4.1 Are there associations between abdominal and MF muscle size and muscle function and measures of physical activity, physical function and quality of life among older adults?

CHAPTER 3. THE ASSESSMENT OF ABDOMINAL AND MULTIFIDUS MUSCLES AND THEIR ROLE IN PHYSICAL FUNCTION IN OLDER ADULTS: A SYSTEMATIC REVIEW



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(Original article included as appendix 11)

3.1 Prelude

Chapter 1 described trunk muscle anatomy, their actions and the potential for ageing to affect these muscles and cause deterioration in physical function in older adults. Furthermore, it found that the validity and reliability of methods of assessment for abdominal and MF muscles established in younger people may not be similarly observed in older people. Features of ageing such as spinal degeneration, increased intramuscular fat infiltrations, increased fibrous tissue content and decreased water content of skeletal muscle, increases the difficulty of assessment of ageing muscles [122, 185] . This chapter has two parts. Firstly, it reproduces the text of a published systematic review to provide holistic picture of the current state knowledge on abdominal and MF muscles and their assessment in older adults. Secondly, the last part of this chapter provides a narrative update of relevant literature published subsequent to the last search date of the systematic review i.e. May 2013. The following text in this chapter up to page 43 (Authors contributions) has been published in the journal Physiotherapy; Cuellar W, Wilson A, Blizzard C, Otahal P, Callisaya M, Jones G, et al. The assessment of abdominal and multifidus muscles and their role in physical function in older adults: a systematic review. Physiotherapy. 2017;103(1):21-39. 2017, 103:21 – 39 [138]. This journal has an impact factor of 3.12 and the paper has been cited in 7 publications.

3.2 Introduction

The muscles of the trunk are essential for normal functional activities such as walking and are involved in the control of balance and posture [8]. Research on the influence of low back pain (LBP) on these muscles forms the basis of rehabilitation and motor control programs used by physiotherapists to address alterations in the function of these muscles [222]. Research has focused on the abdominal (internal oblique (IO), external oblique (EO), rectus abdominis (RA) and transversus abdominis (TrA)) and lumbar multifidus muscles (MF), but predominantly in younger adults. While physical capacity, skeletal muscle mass and strength [5] deteriorate with age (sarcopenia), the age-related changes of trunk muscles and the impact of such changes are poorly understood. A comprehensive summary of the current literature is critical to guide current clinical practice aimed at reducing age-related losses in physical function and to identify evidence gaps for future research.

Electromyography (EMG), ultrasound imaging (USI), computerised tomography (CT) and magnetic resonance imaging (MRI) are commonly used to assess trunk muscle activation,

morphology and function. EMG assesses muscle activation patterns which are associated with muscle function [223]. USI, CT and MRI assess muscle morphology, including thickness and cross-sectional area (CSA), which are associated with the amount of force an individual can develop [224]. CT and MRI can also evaluate muscle composition, which includes muscle density or muscle attenuation (MA). Muscle attenuation is a radiological characteristic used to quantify macroscopic accumulation of intramuscular fat (muscle quality). The greater this accumulation, the lower the attenuation score in Hounsfield units (HU) [165].

The validity and reliability of trunk muscle measurements using EMG and imaging techniques have been reported for younger populations[177, 180], a variety of factors may affect reliability for older adults. The presence of LBP, chronic disease, increases in water content and intramuscular fat accumulation as well as technical issues such as repositioning of the patient for scanning, muscle activation sequences and rate of imaging have the potential to affect reliability of imaging[122]. Concerns regarding the reliability of EMG measures due to problems with task standardization, "out-of-plane" movements and normalization of EMG signals, have also been documented [180]. It is therefore important to determine the validity and reliability of these measures specifically for older adults.

The first aim of this systematic review was to provide a summary of the evidence for changes in function, composition and morphology of the abdominal and MF muscles and the effects of any changes on the physical function of older adults. The second aim was to document the validity and reliability of measurements of abdominal and MF muscles among older adults.

3.3 Methods

3.3.1 Literature search

A systematic literature search was conducted on PubMed, CINAHL, EMBASE and The Cochrane library databases as detailed in supplementary file 2 (Appendix 7).

Inclusion/exclusion criteria:

Studies were included if they:

- Were an observational study or randomised controlled trial assessing abdominal or MF muscles.
- had at least 80% of participants ≥50 years old, or data for ≥50 year olds could be

extracted from published results.

- Used EMG, USI, CT, or MRI to assess abdominal (RA, EO, IO or TrA) or MF muscles.
- Reported:
  - validity/reliability or descriptive data for any those muscles, and/or
  - associations of muscle measures with measures of physical function (excluding bodily functions such as micturition, coughing, sneezing and defecation), and/or
  - associations of muscle measures with other factors including but not limited to age, sex, serum vitamin D, medical conditions and medications.

Studies of post-acute abdominal or post-acute back surgery, animals and cadavers were excluded.

3.3.2 Data collection and analysis

Two reviewers (WAC and TMW) independently screened all titles, abstracts and if required full-text articles for inclusion, with differences resolved by consensus. Two reviewers (WAC and AW) independently extracted data from included studies, with a third reviewer (TW) available to adjudicate any disagreements but this was not needed. Data extracted were participant characteristics (age, body mass index (BMI), gender, ethnicity) and study characteristics (number of participants, inclusion/exclusion criteria, study design, trunk muscles measured, assessment method, adjustment for confounders and study setting). Information on measures of validity/reliability and results of any associations tested between the muscles of interest and other factors were extracted as outcomes.

3.3.3 Assessment of methodological quality of studies

Methodological quality was assessed independently by two reviewers (WAC and AW) by an established approach for systematic reviews of observational studies on musculoskeletal topics [225] modified as appropriate for our topic. Twenty-three criteria assessed internal validity and informativeness of the studies (Supplementary file 3) (Appendix 8). Each criterion was assessed as met (+), not met (-) or unclear (?) based on the descriptions given in Supplementary file 4 (Appendix 9). Studies with a score >60% were considered to be high quality [225].

3.3.4 Best evidence synthesis

The marked methodological heterogeneity of the included studies precluded meta-analysis, so a best evidence synthesis was undertaken. As the first step, studies were grouped according to the condition or population studied, namely healthy older adults and participants with a specific

spinal condition (as described in the individual studies e.g. vertebral fracture or lumbar degenerative kyphosis, and in which LBP was not the primary outcome measure), non-specific low back pain, stroke and other conditions. Studies reporting reliability were also grouped together. Synthesis was performed separately for each of these groups.

The level of evidence was determined using the criteria of Lievense and colleagues [225]: strong evidence - generally consistent findings in multiple high-quality cohort studies; moderate evidence - general consistent findings in one high quality cohort study and 2 or more high quality case-control studies or in three or more high quality case-control/cross-sectional studies; limited evidence – general consistent findings in a single cohort study, in one or two case-control studies or in multiple case-control/cross-sectional studies; conflicting evidence - <75% of the studies reported consistent findings; no evidence - no studies found. Reliability was categorised as per Shrout [226] (≤0.10 = virtually none, 0.11–0.40 = slight, 0.41–0.60 = fair, 0.61–0.80 = moderate, and 0.81–1.0 = substantial).

3.4 Results

Of 2176 potential references, 395 were excluded as duplicates, and 1326 were excluded from abstract and title. A further 427 articles were excluded after full text review, leaving twenty eight included articles (Figure 1) [122, 135, 145, 181, 183, 184, 186, 223, 227-246].

3.4.1 Characteristics of included studies

Sixteen cross-sectional and eleven case-control studies, and one longitudinal observational study, were included (Table 3.1). Fourteen studies used EMG to measure trunk muscle motor activity, reflex latencies, muscle fatigue and postural responses. Six used USI to measure muscle thickness and CSA, two used MRI to measure CSA, and six used CT to measure CSA, muscle density and MA. Twelve studies were of healthy adults, five were of participants with spinal conditions, three were of participants with LBP and six were of participants after stroke. There were single studies of people with Parkinson's disease and with hip osteoarthritis. The number of participants ranged from 3 to 1194 (median = 27) and mean ages ranged from 50 to 88 years. Twenty-two studies (79%) were scored as high quality (Supplementary File 5) (Appendix 10).

3.4.2 Best evidence synthesis

3.4.2.1 Measures of reliability

There was limited evidence that abdominal or MF muscle CSA, density or attenuation of older adults can be reliably measured with CT. There was limited evidence that MF muscle CSA can be reliably measured with MRI. There was limited evidence that abdominal muscle thickness can be reliably measured with USI. There was no evidence of the reliability of EMG measures, abdominal muscle measurements using MRI, MF measurements using USI or of the test-re-test reliability or validity of any modality.

Moderate to substantial intraclass correlation coefficients (ICCs) were reported for CT measurements of abdominal muscle CSA and attenuation and USI measurements of muscle thickness (ICCs ranged from 0.75 - 1.00, Table 3.2). Reliability of CT measurements of MF muscle density and CSA, and MRI measurements of CSA, was also moderate to substantial (ICC = 0.70 - 0.99). One USI study reported a Pearson correlation of r = 0.948 for intra-observer reliability of RA and EO muscle thickness [243], but this is not a recommended reliability measure. One CT study reported a coefficient of variation of less than 5% for measurements of CSA and MA of the EO, IO and MF muscles at the L4-5 vertebral levels [145]. Most reliability measures were obtained from stored images of healthy participants [145, 181, 183, 238, 243, 245], but one study involved participants with spinal conditions [184].

Table 3.1 Characteristics of participants and studies

Author Country Year	N*	Incl/ Excl Criteria	Age (mean, SD)	BMI	Gender M (%)	Ethnicity	Study design	Muscles measured	Assess method	Confounders adjusted	Study setting	Quality score	Quality (%)
Studies of Healthy Adults													
‡ **Anderson (USA 2012)**	100	**Incl: Participants from larger Framingham Heart Study families, residents of Greater New England area, men ≥35 y.o., women ≥40 y.o., weight < 320 pounds Excl: Participants with only 1 parent in the Framingham Heart Study with a father <55 y.o. or a mother <65 y.o.	59.4(14.6) (M) 58.1(13.3) (F)	NS	51	NS	Cross Sectional	RA, EO, IO, LM	CT	Age, sex, height, body mass	Community based, Massachus. area	13/14	93
‡ **Anderson (USA 2013)**	60		78.6(2.7) (M) 78.4 (3.3) (F)	28.4 (4.1) (M) 28 (6.1) (F)	50	NS	Cross Sectional	RA, EO,IO, LM	CT	Age group, sex	Community based	17/20	85
Caix (France 1984)	3	NS	14 ("up to" 20) 34 (21-50) 3 (>50)	NS	69	NS	Cross Sectional	RA, OE, IO TrA	EMG	Sex, age, muscle morphology, PA, PI	NS	4/14	29
Hanada (Canada 2008)	12	Incl: ≥50 years of age. Asymptomatic or LBP> 8 moths Excl: LBP associated with known pathology, spinal fracture or surgery. Previous spinal fracture. MSK, CR, or Neuro conditions, dizziness, pain or recurrent falls.	68.7 (3.5)	27.2 (3.5)	60	NS	Cross Sectional	RA, EO, IO, LM	EMG	NS	Dalhousie University	11/14	79
Hwang (Korea 2008)	15	Incl: healthy volunteers ≤30 y.o. younger group and ≥60 y.o. for elderly group	26.7 (3.3) Y 63.1 (2.7) O	NS	53	NS	Cross Sectional	ES, LM	EMG	NS	NS	9/14	64
Ikezoe (Japan 2012)	41	Excl: Young: Hx of Trunk muscle or bone disease, LBP, spinal surgery. Excl: elderly: Unstable physical condition, Hx of spinal or lower limb surgery, acute Neuro or severe MSK impairment	20(.84) Y 85.7(5.5) IE 87.8(6.3) CBR	22.1 (2.3) Y 20.5 (3.2) IE 16.6 (2.1) CBR	0	Japanese	Cross Sectional	RA, EO, IO, TrA, LM	USI	NS	Nursing home	10/14	71
Kai (Japan 2008)	5	Incl: Old: 68-82 years of age. Young: 19-31 years of age Excl: Old: Hx of Neuro or MSK disorders. Young: NS	22.6(4.4) Y 73(5.7) O	20.6(2.8) Y 21.1(2.2) O	100	NS	Cross Sectional	IO, LM	EMG	NS	NS	8/14	57

N* Number of participants ≥ 50 year; **information obtained from Parikh et al 2007; † classification refers to level of training and running participants were engaged in prior to the study; ‡ These studies were conducted on the same population; NS, Not stated; RA, Rectus abdominis; EO, External oblique; IO, Internal oblique; TrA, Transversus abdominis; LM, lumbar multifidus; Y, Young; O, old; YA, Young adult; YO, young old; OO, old; MA, Middle aged; PA, Physical activity; PAI, Physical activity index; PI, Ponderal index; LBP, low back pain; NLBP, CLBP, chronic low back pain; No low back pain; Abdo, Abdominal; MSK, Musculoskeletal; CR, Cardio-respiratory; Neuro, Neurological; Hx, History; IE, Independent elderly; CBR, Chronic bed ridden; PT, Patients; ADL, Activities of daily living; Inter, Intermediate; Ma. Middle aged; degen, Degeneration; Prospect, prospective; observatio, Observational; Longitud, Longitudinal; MAS, Modified Ashworth Scale; OA, Osteoarthritis

Author Country Year	N*	Incl/ Excl Criteria	Age (mean, SD)	BMI	Gender M (%)	Ethnicity	Study design	Muscles measured	Assess method	Confounders adjusted	Study setting	Quality score	Quality (%)
McGill (Canada 1999)	12	Incl: Participants in good physical condition. Excl: Hx of disabling low back injury, recent recurrent pain	69(3.5)	NS	42	NS	Cross Sectional	RA, EO, IO, LM	EMG	NS	NS	8/14	57
Oguri (Japan 2004)	28	Incl: middle-aged long distance runners and untrained individuals.	† 61.4(3) High 62.9 (2.7) Inter 61.4 (2.8) Low	21.8 (1.8) High 22.7 (2.4) Inter 23 (1.6) Low	100	Japanese	Cross Sectional	RA, EO	USI	Height, length of extremities	NS	10/14	71
Ota (Japan 2012)	51	Incl: Healthy physically active women Excl: History of trunk or lower extremity surgery or Neuro impairment, paresis of the lower limbs or a severe MSK impairment.	21(1.1) Y 34.5(5.8) YA 58 (4.5) MA 70.6(2.6) YO 79.7(2.6) OO	NS	0	Japanese	Cross Sectional	RA, EO, IO, TrA	USI	Age, height, weight	NS	10/14	71
Stetts (USA 2009)	12	Incl: Healthy aging adults Excl: LBP, history of abdominal, spinal or lower limb surgery. Respiratory or neurological disorders. Structural scoliosis, urinary incontinence, BMI>30, pacemaker, Mini Mental State Exam <24, severe OA.	72(9.36)	25.9 (2.96)	25	NS	Cross Sectional	TrA, IO, EO	USI	NS	NS	10/14	71
Stokes (UK 2005)	46	Excl: Hx of Neuro, neuromuscular, rheumatological or systemic disease. Pregnancy, medication which may affect muscle size, any skin condition or wound in the area to be scanned. Lifetime LBP interfering with ADL's. Lifetime Hx of spinal fractures, lumbar surgery, scoliosis or spondylolisthesis	L4 40.1 (13) Male, 34.2 (12.8) Female L5 39 (13) Male 31 (11.7) Female	L4 25.8 (3.2) Male 23 (3.1) Female L5 25.7 (2.9) Male 22.3 (2.2) Female	L4 43 L5 49	NS	Cross Sectional	LM	USI	NS	NS	10/14	71
Studies of participants with spinal conditions													
Briggs (Australia 2007)	25	Incl: osteoporosis Excl: NS	68.4 (6.7) Fracture 64.0 (8.9) No-fracture	26.1(4) Fracture 24(3.3) No-fracture	0	NS	Cross Sectional	MF	EMG	NS	NS	10/14	71
‡Kalichman (USA 2010)	91	**Incl: Participants from larger Framingham Heart Study families, residents of Greater New England area, men ≥35 y.o., women ≥40 y.o., weight < 320 pounds	54.4(9.3) LBP 52.2(11.1) NLBP	28.7(5.5) LBP 27.6(4.9) NLBP	49 LBP 57 NLBP	NS	Cross Sectional	MF	CT	Spinal degen, age, sex, BMI	NS	12/14	86

N* Number of participants ≥ 50 year; **information obtained from Parikh et al 2007; † classification refers to level of training and running participants were engaged in prior to the study; ‡ These studies were conducted on the same population; NS, Not stated; RA, Rectus abdominis; EO, External oblique; IO, Internal oblique; TrA, Transversus abdominis; LM, lumbar multifidus; Y, Young; O, old; YA, Young adult; YO, young old; OO, old; MA, Middle aged; PA, Physical activity; PAI, Physical activity index; PI, Ponderal index; LBP, low back pain; NLBP, CLBP, chronic low back pain; No low back pain; Abdo, Abdominal; MSK, Musculoskeletal; CR, Cardio-respiratory; Neuro, Neurological; Hx, History; IE, Independent elderly; CBR, Chronic bed ridden; PT, Patients; ADL, Activities of daily living; Inter, Intermediate; Ma. Middle aged; degen, Degeneration; Prospect, prospective; observatio, Observational; Longitud, Longitudinal; MAS, Modified Ashworth Scale; OA, Osteoarthritis

Author Country Year	N*	Incl/ Excl Criteria	Age (mean, SD)	BMI	Gender M (%)	Ethnicity	Study design	Muscles measured	Assess method	Confounders adjusted	Study setting	Quality score	Quality (%)
‡Kalichman (USA 2011)	91	**Excl: Participants with only 1 parent in the Framingham Heart Study with a father <55 y.o. or a mother <65 y.o.	50-59 n=55 60+ n=36	NS	58	NS	Cross Sectional	MF	CT	Age, sex, BMI	NS	12/14	86
Kang (Korea 2007)	108	Incl: PT: Patients with Lumbar degenerative kyphosis (LDK) who underwent corrective surgery from 1997 -2003. Incl: Controls: Mechanical chronic LBP with or without disc protrusion Excl: Controls: LDK, isthmic spondylolisthesis, spinal fracture, tumour, infection, Hx of previous surgery or presence of lumbar scoliosis exceeding 10 degrees	60.19(5.89) PT 60.15(6.23) Controls	24.19(3.10) PT 26.09(2.9) Controls	0	Korean	Retrospect case control	MF	MRI	Weight, BMI	Hospital	15/16	94
Shafaq (Japan 2012)	107	Incl: PT: Surgery for Lumbar spinal stenosis (LSS) with Degenerative lumbar scoliosis (DSL) Incl: Controls: Surgery for LSS without DSL Excl: adolescent idiopathic scoliosis, previous lumbar surgery, pyogenic scoliosis, or vertebral fracture in the lumbar spine.	70.2(7.3) PT 69.1(7.1) Controls	NS	23 PT 24 Controls	Japanese	Case control	MF	MRI	NS	Hospital	14/16	86
Studies of participants with low back pain													
Hanada (Canada 2011)	18	Incl: 50 y.o. or older and LBP>8/12 for LBP group Excl: LBP associated with unknown pathology, radicular syndrome or cauda equina, spinal fracture, surgery or nonspecific LBP	61.4 (9.8) CLBP 64.9 (8.8) NLBP	26 (6.6) CLBP 25.6 (2.4) NLBP	44	NS	Cross Sectional	RA, IO, MF	EMG	NS	NS	10/14	71
Hicks (USA 2005)	1515	Incl: 70-79 y.o. no difficulty walking 1/4 mile, walking up 10 steps or performing ADL's. no cancer or plans to move from area for 3 years	73.72 (2.88) NLBP 73.6(2.82) LBP	27.32 (4.58) NLBP 28.86 (5.36) LBP	48	44% Black 56% White	Longitud observatio	RA, lateral Abdo and lumbar Paraspinal	CT	Age, sex, height, race, body fat, muscle CSA, PA, disease status, LBP	Community	16/19	84

N* Number of participants ≥ 50 year; **information obtained from Parikh et al 2007; † classification refers to level of training and running participants were engaged in prior to the study; ‡ These studies were conducted on the same population; NS, Not stated; RA, Rectus abdominis; EO, External oblique; IO, Internal oblique; TrA, Transversus abdominis; LM, lumbar multifidus; Y, Young; O, old; YA, Young adult; YO, young old; OO, old; MA, Middle aged; PA, Physical activity; PAI, Physical activity index; PI, Ponderal index; LBP, low back pain; NLBP, CLBP, chronic low back pain; No low back pain; Abdo, Abdominal; MSK, Musculoskeletal; CR, Cardio-respiratory; Neuro, Neurological; Hx, History; IE, Independent elderly; CBR, Chronic bed ridden; PT, Patients; ADL, Activities of daily living; Inter, Intermediate; Ma. Middle aged; degen, Degeneration; Prospect, prospective; observatio, Observational; Longitud, Longitudinal; MAS, Modified Ashworth Scale; OA, Osteoarthritis

Author Country Year	N*	Incl/ Excl Criteria	Age (mean, SD)	BMI	Gender M (%)	Ethnicity	Study design	Muscles measured	Assess method	Confounders adjusted	Study setting	Quality score	Quality (%)
Takahashi (Japan 2007)	20	Incl: PT: motion induced intermittent LBP (MILBP) Controls: No Hx of LBP or sciatica Excl: NS	75.7(5.14) MILBP 74.4(7.9) Controls	NS	0 MILBP 0 Controls	NS	Case control	RA, ES	EMG	NS	Hospital	8/14	57
Studies of participants after stroke													
Dickstein (Israel 2000)	26	Incl: PT: Communicative, "clear-minded" patients with hemiparesis or hemiplegia following a single unilateral stroke Incl: Controls: Healthy controls Excl: Sensory or motor deficiencies unrelated to stroke	74.2 (9.9) PT 67 (9.6) Controls	NS	54 PT 46 Controls	NS	Case control	RA, EO	EMG	NS	Rehabilitation hospital	10/14	71
Dickstein (Israel 2004a)	80	Incl: PT: a-hemiparesis (or plegia) following first unilateral stroke in the territory of the middle cerebral artery, b- sufficiently stable physical health condition to participate in study c- able to sit without support. Incl: Controls: Healthy controls Excl: cognitive or communication deficits Neuro or MSK disorders unrelated to stroke.	72 (9) PT 71(9) Controls	NS	54 PT 43 Controls	NS	Case control	ES, RA, EO	EMG	NS	Geriatric rehabilitation hospital	10/14	71
Dickstein (Israel 2004b)	80	Incl: PT: hemiparetic patients Incl: Controls: Healthy controls	72(9) PT 71(9) Controls	Ns	54 PT 43 Controls	NS	Case control	RA, EO	EMG	NS	Geriatric rehabilitation hospital	9/14	64

N* Number of participants ≥ 50 year; **information obtained from Parikh et al 2007; † classification refers to level of training and running participants were engaged in prior to the study; ‡ These studies were conducted on the same population; NS, Not stated; RA, Rectus abdominis; EO, External oblique; IO, Internal oblique; TrA, Transversus abdominis; LM, lumbar multifidus; Y, Young; O, old; YA, Young adult; YO, young old; OO, old; MA, Middle aged; PA, Physical activity; PAI, Physical activity index; PI, Ponderal index; LBP, low back pain; NLBP, CLBP, chronic low back pain; No low back pain; Abdo, Abdominal; MSK, Musculoskeletal; CR, Cardio-respiratory; Neuro, Neurological; Hx, History; IE, Independent elderly; CBR, Chronic bed ridden; PT, Patients; ADL, Activities of daily living; Inter, Intermediate; Ma. Middle aged; degen, Degeneration; Prospect, prospective; observatio, Observational; Longitud, Longitudinal; MAS, Modified Ashworth Scale; OA, Osteoarthritis

Author Country Year	N*	Incl/ Excl Criteria	Age (mean, SD)	BMI	Gender M (%)	Ethnicity	Study design	Muscles measured	Assess method	Confounders adjusted	Study setting	Quality score	Quality (%)
Kafri (Israel 2005)	31	Incl: PT: hemiparesis due to first ischemic stroke Incl: Controls: community dwelling individuals free of Neuro or MSK disorders that could interfere with side rolling Excl: aphasia, previous Neuro or orthopaedic disorders limiting performance of side rolling.	71.9(5.8) PT 65.3(9.1) Controls	NS	65 PT 50 Controls	NS	Case control	EO	EMG	NS	NS	10/14	71
Marcucci (Brazil 2007)	16	Incl: PT: post unilateral stroke Hemiparesis, Ashworth scale spasticity 1-4, Bartel index >85, able to ambulate with or without assistance Incl: Controls: individuals matched by sex, age, height and weight, free of Neuro symptoms Excl: neurological syndromes preventing them from participating in the study	58.7(9.3) PT 59.5(11.3) Controls	25 PT 24.8 Controls	75 PT 75 Controls	NS	Case control	RA, EO	EMG	NS	NS	9/14	64
Pereira (Brazil 2011)	24	Incl: Unilateral stroke, able to walk alone or with help. MAS score 1-3 and able to perform exercises. Incl: Controls: Healthy controls Excl: Neuro or MSK disorders unrelated to stroke, obesity or cognitive deficits	57.5(8.5) PT 58.7(9.7) Controls	24.7 (2.7) PT 25.1 (2.4) Controls	58 PT 58 Controls	NS	Case control	RA, OE, ES	EMG	NS	NS	9/14	64
Other studies													
Fukumoto (Japan 2012)	40	Incl: PT: unilateral or bilateral Hip OA Incl: controls: Healthy women without hip OA Excl: Hx of limb or back surgery, symptoms affecting knees, ankles or back. RA vestibular, central or peripheral nervous system problems. Dementia	56.8 (6.4) PT 57.7 (6.4) Controls	22.1 (3.8) PT 21.6 (2.6) Controls	0 PT 0 Controls	Japanese	Case control	RA, EO, IO, TrA	USI	NS	Kyoto's university hospital	12/14	86

N* Number of participants ≥ 50 year; **information obtained from Parikh et al 2007; † classification refers to level of training and running participants were engaged in prior to the study; ‡ These studies were conducted on the same population; NS, Not stated; RA, Rectus abdominis; EO, External oblique; IO, Internal oblique; TrA, Transversus abdominis; LM, lumbar multifidus; Y, Young; O, old; YA, Young adult; YO, young old; OO, old; MA, Middle aged; PA, Physical activity; PAI, Physical activity index; PI, Ponderal index; LBP, low back pain; NLBP, CLBP, chronic low back pain; No low back pain; Abdo, Abdominal; MSK, Musculoskeletal; CR, Cardio-respiratory; Neuro, Neurological; Hx, History; IE, Independent elderly; CBR, Chronic bed ridden; PT, Patients; ADL, Activities of daily living; Inter, Intermediate; Ma. Middle aged; degen, Degeneration; Prospect, prospective; observatio, Observational; Longitud, Longitudinal; MAS, Modified Ashworth Scale; OA, Osteoarthritis

Author Country Year	N*	Incl/ Excl Criteria	Age (mean, SD)	BMI	Gender M (%)	Ethnicity	Study design	Muscles measured	Assess method	Confounders adjusted	Study setting	Quality score	Quality (%)
Kataoka (Japan 2012)	16	Incl: PT: Parkinson's disease (PD) with painful abdominal contractions (PAC). Incl: Controls: PD without PAC Excl: multisystem atrophy, another atypical parkisonian syndrome, non-reducible spine flexion and large vessel disease, infarction or tumour on cranial MRI	77 and 80 Pat Age-matched controls	21.3 and 22.8 PT 21.3 (2.5) Controls	50	Japanese	Case control	RA	CT	NS	NS	3/17	18

N* Number of participants ≥ 50 year; **information obtained from Parikh et al 2007; † classification refers to level of training and running participants were engaged in prior to the study; ‡ These studies were conducted on the same population; NS, Not stated; RA, Rectus abdominis; EO, External oblique; IO, Internal oblique; TrA, Transversus abdominis; LM, lumbar multifidus; Y, Young; O, old; YA, Young adult; YO, young old; OO, old; MA, Middle aged; PA, Physical activity; PAI, Physical activity index; PI, Ponderal index; LBP, low back pain; NLBP, CLBP, chronic low back pain; No low back pain; Abdo, Abdominal; MSK, Musculoskeletal; CR, Cardio-respiratory; Neuro, Neurological; Hx, History; IE, Independent elderly; CBR, Chronic bed ridden; PT, Patients; ADL, Activities of daily living; Inter, Intermediate; Ma. Middle aged; degen, Degeneration; Prospect, prospective; observatio, Observational; Longitud, Longitudinal; MAS, Modified Ashworth Scale; OA, Osteoarthritis

Table 3.2 Reliability measures

Author	Assessment Modality	Measurements tested	Reliability Coefficients	Reliability Type
Anderson 2013	CT	CSA EO, IO, MF taken at L3	ICC >0.75	Intra-observer
		CSA EO, IO, MF taken at L3	ICC >0.75	Inter-observer
Hicks 2005	CT	Muscle CSA and attenuation at level L4-L5 EO, IO, MF	CV<5%	Not stated
Kalichman 2010	CT	Density of MF at levels L3-L5	ICC = 0.94-0.99	Intra-observer
		Density of MF at levels L3-L5	ICC = 0.70 – 0.97	Inter-observer
Kang 2007	MRI	CSA MF taken at level L4-L5	ICC = 0.89 – 0.92	Intra-observer
Shafaq 2012	MRI	CSA MF, spinal level at which image was taken was not specified	ICC = 0.98	Intra-observer
		CSA MF, spinal level at which image was taken was not specified	ICC = 0.97	Inter-observer
Oguri 2004	USI	Muscle thickness RA taken 3 cm distal to and right of the umbilicus	r = 0.948	Intra-observer
		Muscle thickness EO taken 10 cm on the "diagonal rear" of iliocostalis	r = 0.948	Intra-observer
Stetts 2009	USI	Muscle thickness EO, IO, TrA transducer placed in a transverse plane halfway between ASIS and the lower rib cage, along the axillary line	ICC = 0.95-1.00	Intra-observer
		Muscle thickness EO, IO, TrA transducer placed in a transverse plane halfway between ASIS and the lower rib cage, along the axillary line	ICC = 0.77-0.97	Inter-observer

3.4.2.2 Evidence in healthy adults

There was limited evidence for a detrimental association between age and abdominal or MF muscle morphology (MA, thickness or CSA) in healthy adults, although not all studies were consistent (Table 3.3). Data for RA, EO and IO were most consistent, with significantly smaller RA (27-38%), EO (23-47%) and IO (26-48%) muscles in healthy independent older women compared to younger controls [186, 244] and these muscles being smaller with increasing age[227]. Abdominal muscle MA was also, 33% lower in adults ≥75 years compared with younger controls (30-50 years) [181]. Associations of age with MF and TrA were less consistent. In most studies age-related differences in muscle thickness or CSA were small or not statistically significant for the TrA (12-23%) and MF (12%) muscles [122, 186, 244] but MF MA was 51% lower in adults ≥75 years compared with younger controls (30-50 years) [181] and age was associated with smaller MF CSA in one study [227].

There was conflicting evidence to support an association between age and EMG measures of abdominal muscles. Hwang et al. reported a 45% decrease in reflex latency of the MF muscle of older compared to younger adults when sudden loads were applied to the upper limbs [235]. Hanada et al. found lower muscle activation of abdominal and MF muscles during hip/knee movements by older adults than in normative data from younger adults [233]. Caix et al. reported much lower abdominal muscle motor activity among older than younger adults during contralateral axial twisting of the trunk [229]. Contrary to those studies, McGill et al. reported higher motor activation of abdominal muscles among older adults during movements of the trunk [242], and Kai et al. found no differences between activation of the IO and MF muscles of older and young adults controls when moving from a two-leg to a one-leg standing position[237].

There was conflicting evidence for an association between abdominal or MF muscle measures and physical activity (PA). Oguri et al. found no difference in thickness of the rectus abdominis muscle in endurance compared to untrained men [243]. Conversely, in other studies individuals with higher levels of physical activity had better muscle quality [181] and, at the extreme end of inactivity, chronically bedridden female nursing home residents had greater declines in muscle thickness in abdominal (~33%) and MF (~2%) muscles compared with independent residents [186]. No studies in healthy adults investigated associations between trunk muscle measures and any aspect of physical function included in this review (see inclusion criteria).

3.4.2.3 Participants with spinal conditions

There was limited evidence for an association between spinal conditions and detrimental changes in MF muscle morphology or muscle activation. Nevertheless, some evidence of a detrimental effect was found in every study of both muscle morphology and muscle activation (Table 3.4). MF muscle activation was delayed in older adults with osteoporotic vertebral fractures [228]. MF muscle CSA was decreased by 36% in older adults with lumbar degeneration [183]. Similarly, Shafaq et al. reported decreases of MF muscle CSA on the concave side of older adult patients with degenerative lumbar scoliosis (10-22%) and on the affected side of patients with lumbar spinal stenosis (15-20%) with increases in muscle fat infiltrations in both populations [184]. Kalichman et al. reported associations of age and moderate to severe facet joint osteoarthritis with low MF density [238] and an association between increased lumbar lordosis and low MF density [239].

Table 3.3 Studies of healthy older individuals

Author	Factors tested	Results	Statistical methods	Summary
Anderson (USA 2012) CT [227]	RA, IO, EO and MF CSA at Levels L2-L5 and association with age, sex and body mass	Among 36-87 year olds, abdominal and MF muscle CSA was negatively associated with sex and age and positively associated with body mass. The regression models explained 52-65% of RA, 20-64% of EO, 36-63% of IO and 22-39% of MF CSA variability.	Linear regression	Muscle CSA is smaller for women, older subjects, and those of lesser weight
Anderson (USA 2013) CT [181]	Muscle attenuation (MA) of abdominal and MF muscles and association with age, sex and PA	**At L3 level**: MA was lower among adults ≥75 years old (-15.9(1.07) HU, P<0.001) compared with adults 30-50 years and lower in women (-6.9(0.46) HU, p<0.001) compared with men. There was a significant association between PA and low MA (effect sizes not reported)	ANOVA, linear regressions, ANCOVA	RA, EO, IO and MF muscle attenuation was lower among older adults, women and people with decreased physical activity.
Caix (France 1984) EMG [229]	Abdominal muscle motor performance according to age, sex, mass and physical activity	Compared with the younger group ("up to 20" y.o.), the older group (>50 y.o.) showed decreased motor activity of RA in tonus (19%), posture (66%) and movement (98%). The flat abdominals showed decreased motor activity in tonus (64%), posture (80%) and movement (97%).	Not stated	Abdominal muscle activation was lower for participants 50 years or older
Hanada (Canada 2008) EMG [233]	Abdominal and MF muscle response to change in load	During hip/knee flexion/extension exercises, abdominal muscles activation amplitudes varied according to level (1-3) of difficulty (15% - 34% of max voluntary isometric contraction (MVIC)). Muscle activation amplitudes of MF was less than 10% MVIC and there were little changes between levels of difficulty (7(3)% - 7(3)% MVIC)	None	Among healthy adults (65-80 years), abdominal muscle activation amplitudes were low to moderate, depending on the level of exercise difficulty. There is low MF muscle activation irrespective of level of exercise difficulty.
Hwang (Korea 2008) EMG [235]	Reflex latencies, flexion movement and flexion moment of the trunk and association with age and upper limb loading	**During UL sudden loads:** significant age-related delay of multifidus reflex latency during expected loads (mean=-26.08, 95% CI -42.45 - -9.71 ms, p=0.0026.	ANOVA	Age-related delay in multifidus muscle reflex activation and trunk flexion movement in response to sudden loading

RA, Rectus abdominis; EO, External oblique; IO, internal oblique; TrA, Transversus abdominis; MF, Lumbar multifidus, y.o., years old; MF, Lumbar multifidus; CSA, Cross sectional area; MA, Muscle attenuation; PA, physical activity; HU, Hounsfield units; CI, confidence intervals, AP, Antero-posterior; Lat, lateral dimension; mm, Millimetres

Author	Factors tested	Results	Statistical methods	Summary
Ikezoe (Japan 2012) USI [186]	Abdominal and MF muscles of elderly women and association with age and inactivity	A significant decrease in muscle thickness of RA (36%, 51%), EO (40%, 66%) and IO (48%, 57%) in independent and chronic bedridden elderly women correspondingly, was found compared with the young women group. A significant decrease in muscle thickness of TrA (52%), MF (30%) was found only in chronically bedridden elderly women compared with the young women group	ANOVA and Mann-Whitney U-tests	Age-related muscle atrophy was smallest for the deep trunk muscles (TrA and MF) of elderly women. Chronically bedridden elderly women had greater decrease in all trunk muscle thickness compared with independent elderly.
Kai (Japan 2008) EMG [237]	Muscular activity of left IO and MF while moving from two-leg standing to one-leg standing in healthy elderly (n=5) compared with young (n=8) subjects	Higher levels of muscle activity were observed in IO and MF in the young person group, compared with the healthy elderly group. However, the differences were not statistically significant in this small sample. No effect sizes were reported.	Mann-Whitney U-test	No significant difference in IO or multifidus muscle activation between young and older adults during the two-leg standing to one-leg standing task
McGill (Canada 1999) EMG [242]	RA, EO and IO muscle activation and association with age and trunk movement	RA, EO and IO muscle activity was greater in the elderly group compared with a young control group during the flexion ($p=0.0001$) and lateral bending ($p=0.0001$) tasks, but not the axial twisting ($p>0.05$) task. No effect sizes were reported	Unclear	Greater abdominal muscle activation during trunk flexion and lateral bending tasks among elderly subjects, compared with younger subjects
Oguri (Japan 2004) USI [243]	RA and EO muscle thickness and association with running training levels	Ra muscle thickness was not significantly correlated ($r=0.326$) with weekly training distance. No significant difference was found between mean RA muscle thickness of high level (7.09 mm), intermediate (6.3 mm) or untrained groups (6.3 mm). EO muscle thickness results were not reported.	ANOVA, Tukey's post hoc test, Pearson correlation.	There was no significant difference in RA muscle thickness among older men despite differences in running training levels
Ota (Japan 2012) USI [244]	RA, EO, IO and TrA muscle thickness and association with age	Muscle thickness (mm) was significantly smaller in older subjects for RA (27 (16) % to 38(20) % $p<0.01$), EO (23(13) % to 46(17) % $p<0.05$)) and IO (26(17) % to 47(18) % $p<0.05$)), compared with young controls. There was no significant age effect on TrA (19(17)% to 23(25)% $p>0.05$))	ANCOVA, ANOVA, Tukey's post hoc test	Age-related decrease in RA, IO and EO muscle thickness. Non-significant decrease in TrA muscle thickness

RA, Rectus abdominis; EO, External oblique; IO, internal oblique; TrA, Transversus abdominis; MF, Lumbar multifidus, y.o., years old; MF, Lumbar multifidus; CSA, Cross sectional area; MA, Muscle attenuation; PA, physical activity; HU, Hounsfield units; CI, confidence intervals, AP, Antero-posterior; Lat, lateral dimension; mm, Millimetres

Author	Factors tested	Results	Statistical methods	Summary
Stokes (UK 2005) USI [122]	CSA and shape of multifidus and association with age	Significant difference in MF shape ratio (AP/Lat) at L5 between the 20-29 y.o. (0.89(0.11)) and the 50-69 y.o. (1.12(0.14)) male groups (p=0.0001). No significant age-related change in CSA of MF and no significant differences of MF symmetry between age groups. However, specific data from the 50-69 age group was not provided.	t-test	Significant difference in shape of multifidus between young and older adults. No significant difference in MF CSA or symmetry at L4 and L5 levels

RA, Rectus abdominis; EO, External oblique; IO, internal oblique; TrA, Transversus abdominis; MF, Lumbar multifidus, y.o., years old; MF, Lumbar multifidus; CSA, Cross sectional area; MA, Muscle attenuation; PA, physical activity; HU, Hounsfield units; CI, confidence intervals, AP, Antero-posterior; Lat, lateral dimension; mm, Millimetres

3.4.2.4 Participants with LBP

There was limited evidence for an association between MF muscle attenuation and LBP, conflicting evidence for an association between alterations in abdominal or MF muscle activation and LBP and limited evidence supporting there being no association between muscle size and LBP (Table 3.5).

Longitudinally, trunk MA but not muscle area was positively associated with physical functional capacity assessed by the Health ABC Physical Performance Battery [145], with a stronger association for people with than without moderate to severe LBP. [145]. Results from the two EMG studies were mixed. Bilateral muscle activation was lower in the RA and higher in the MF muscle with some side differences in IO muscle activity during gait, for older adults with non-specific chronic LBP compared with controls without LBP [234]. Takahashi et al. reported no differences in RA muscle fatigue with mechanical loading among older women with "motion-induced intermittent LBP" compared with controls [246].

3.4.2.5 Participants after stroke

There was conflicting evidence for an association between alterations in abdominal muscle activation and stroke. All studies of patients after stroke used EMG and results were inconsistent (Table 3.6). Comparing the affected to the non-affected side, some studies reported no difference in symmetry index between groups of patients with hemiparesis and healthy controls or side differences for activation of the RA[135, 231, 236] or EO muscles [230, 236]. Others found either decreased [135, 231] or increased [223, 241] RA and EO muscle activity on the affected side, during movements of the trunk or hip joint.

3.4.2.6 Other studies

Only single studies examined associations between abdominal muscle thickness and hip osteoarthritis and painful abdominal contractions among patients with Parkinson's disease (Table 3.5). Patients with hip osteoarthritis had 3-6% thinner abdominal muscles compared with healthy controls [232]. Kataoka et al. reported greater RA thickness for two patients with Parkinson's disease affected by painful abdominal contractions, compared with controls without painful contractions [240].

Table 3.4 Studies of participants with spinal conditions

Author	Factors tested	Results	Statistical methods	Summary
Briggs (Australia 2007) EMG [228]	Associations between vertebral fracture and paraspinal muscle recruitment of subjects with osteoporosis	The time to initiate postural response differed between the non-fracture (epoch 4 = 50-25 ms before deltoid onset) and fracture (epoch 5 = 25-0 ms before deltoid onset) groups.	t-tests, Mann-Whitney U-test, ANOVA, Sharpened Bonferroni post hoc test	Paravertebral muscle activation is delayed among older adults with osteoporotic vertebral fractures
Kalichman (USA 2010) CT [238]	Associations between different lumbar spine degenerative features and density of the MF muscle	Density of MF decreases with age ($p<0.0001$) in people with spinal degeneration features (50-59 y.o. 32.8% of subjects and >60 y.o. 68.8% of subjects). Moderate to severe facet joint OA was associated with decreased density of multifidus (odds ratio 3.68, CI 1.36 - 9.977).	Chi-square test, t-test, Cochrane-Armitage trend test, logistic regression	Significant association between LBP and presence of facet joint OA and decreased density of multifidus
Kalichman (USA 2011) CT [239]	Associations of CT-evaluated lumbar lordosis and density of multifidus	After adjusting for age, sex and BMI, lumbar lordosis angle was positively associated ($p<0.05$) with density of multifidus (odd ratio 1.06, 95% CI 1.01 - 1.11)	t-test, linear regression, logistic regression	Lumbar lordosis angle positively associated with density of multifidus
Kang (Korea 2007) MRI [183]	Paraspinal muscle wasting of lumbar degenerative kyphosis (LDK) patients compared with chronic low back pain (CLBP) patients	MF muscle CSA was smaller (36.3%, $p<0.0001$) in the LDK group compared with the CLBP group	ANOVA, logistic regression, Chi-square test	Older adults with lumbar degenerative kyphosis had significantly smaller MF muscle CSA, compared with CLBP patients
Shafaq (Japan 2012) MRI [184]	Muscle degeneration of patients with lumbar spinal stenosis (LSS) with and without degenerative lumbar scoliosis (DLS)	In the DLS group CSA of MF was smaller on the concave side L3-5 (CI 51.79 59.21 $p=0.035$), L4-5 (CI 60.52 70.48 $p= 0.008$) and L5-S1 (CI 72.70 82.10 $p=0.0001$). In the LSS group with unilateral radiculopathy CSA of MF was smaller on symptomatic side L4-5 (CI 61.37 70.02 $p= 0.007$) and L5-S1 (CI 75.40 84.00 $p= 0.001$). Increases in fat infiltrations in both populations ranging from 2% to 28.3% in the lower spinal levels	Mann-Whitney test, Chi-square test, paired t–test, Pearson correlation	Smaller MF CSA on concave side of DLS patients and on the affected side of LSS patients with unilateral radiculopathy. increases in fat infiltrations in both populations at all spinal levels

MF, Lumbar Multifidus; epoch, “The time to initiate a postural response in which EMG amplitude increases above baseline”; OA, osteoarthritis; LBP, low back pain; CSA, cross-sectional area

Table 3.5 Studies of participants with low back pain and other studies

Author	Factors tested	Results	Statistical methods	Summary
Hanada (Canada 2011) EMG [234]	RA, IO and MF muscle activation amplitudes during gait and association with low back pain	**Compared with the control group, the LBP group:** had lower muscle activation levels of their RA on the right (4% MVIC, P<0.001) and left (7% MVIC, p<0.001) sides, MF muscle activation was greater on the right (10% MVIC) and left (5% MVIC). Significant activation differences were observed in right IO depending on the phase of gait they were measured and left IO muscle activation levels were not significantly different.	t-test, ANOVA, Tukey's post test	Depending on the phase of gait, there were altered RA, IO and multifidus muscle activation levels of older adults with low back pain (LBP) during gait
Hicks (USA 2005) CT [145]	Longitudinal associations between trunk muscle composition, back pain (LBP) and physical function	Trunk muscles MA lower but muscle area was similar in those with compared to without severe LBP). Abdominal and paraspinal muscle attenuation was a significant predictor of composite functional scores (β=0.006, p<0.01). Significant interaction between trunk muscle attenuation and back pain status in predicting physical function for no/mild pain group (β=0.005, p=0.043) and moderate/extreme pain (β=0.011, p=0.011)	Linear regression, t-tests	Positive longitudinal association between abdominal and paraspinal muscle attenuation, back pain status and physical function among older adults with low back pain. No interaction between trunk muscle CSA and back pain status.
Takahashi (Japan 2007) EMG [246]	Effect of mechanical load on RA muscle fatigue	RA muscle fatigue was not induced in either controls (-5.3(12.3) MPF (%/min), 95% CI -14.09 - 3.49) or low back pain group (-1.5(15.0) MPF (%/min) between 30-60 seconds after loading, 95% CI -12.23 - 9.23). (CI values are for the difference of absolute values between groups)	ANOVA, Mann-Whitney U-test	No significant changes in RA muscle fatigue with loading in older participants with LBP or those without LBP
Other Studies				
Fukumoto (Japan 2012) USI [232]	Abdominal muscle thickness and association with hip osteoarthritis	Compared with healthy controls, abdominal muscles in the OA group were: RA 6%, IO 5% and TrA 3% thinner. However, EO was thicker by 12%. These differences were of no statistical significance in this small sample group	Mann-Whitney U-test	No significant difference in abdominal muscle thickness, except for EO, between individuals with hip OA and healthy individuals
Kataoka (Japan 2012) CT [240]	Activation and muscle thickness in Parkinson's patients with painful abdominal contractions (PAC)	Constant hypertonic activity and greater muscle thickness (mm) of RA (48% L4 and 49% L5 vertebral level) in the 2 patients with PAC compared with 14 controls.	Not stated	Constant hypertonic activity was demonstrated in the rectus abdominis muscle of Parkinson's subjects with painful abdominal contraction

MF, Lumbar Multifidus; epoch, "The time to initiate a postural response in which EMG amplitude increases above baseline"; OA, osteoarthritis; LBP, low back pain; CSA, cross-sectional area

Table 3.6 Studies of participants after stroke

Author	Factors tested	Results	Statistical methods	Summary
Dickstein (Israel 2000) EMG [230]	Bilateral activity of RA and EO muscles during basic symmetrical movements and association with hemiparesis	No significant difference in muscle activation of RA (0.85(0.1) - 0.81(0.2), p>0.05) or EO (0.71(0.1) - 0.64(0.2), p>0.05) between healthy and hemiparetic subjects. No significant difference in muscle activation RA (0.66(0.15) - 0.63(0.21, p>0.05) or EO (0.71(0.13) - 0.59(0.28), p>0.05) between the paretic and non-paretic sides	ANOVA, t-test	No differences in RA or EO muscle activation of hemiparetic subjects compared with healthy individuals
Dickstein (Israel 2004a) EMG [231]	Function of RA and EO in voluntary trunk movements and association with stroke	Lower RA and EO muscle activation latency in patients compared with controls ($F(1,69) = 3.96$, $p<0.05$). In the patient group, SI of the RA muscle was significantly lower -17(30) % (concentric), -15(35) % (eccentric) compared with the control group 2(22) %, -1(22) %. SI of EO between patients and controls was not significant.	ANOVA, t-test	Impairment of rectus abdominis muscle function on paretic side and also EO to a lesser degree
Dickstein (Israel 2004b) EMG [135]	RA and EO muscle activation and association with hemiparesis	No significant differences in RA anticipatory muscle activation between hemiparetic and control subjects or between sides on hemiparetic subjects. Reduced EO muscle activation on the hemiparetic side ($F(1,74) = 4.6$, $p<0.04$). Significant difference in symmetry activation of EO on the paretic side of patients compared with corresponding side of controls ($t(74) = 4.84$, $p<0.0001$). No significant difference in RA SI between groups.	ANOVA, linear regression	No difference in anticipatory muscle activation for RA. Reduced EO muscle activation on hemiparetic side.
Kafri (Israel 2005) EMG [236]	EO muscle activation during side rolling from supine lying position and association with hemiparesis	In hemiparetic subjects, symmetry index of EO muscle activation on the paretic side, was comparable or lower -0.22(0.22) than the non-paretic side 0(0.24), but not significantly different	Paired t-test	Among post stroke patients, EO muscle activation symmetry was comparable between paretic and non-paretic sides when rolling from supine to side lying
Marcucci (Brazil 2007) EMG [241]	RA and EO muscle behaviour and association with hemiparesis	During MVIC there were no statistically significant differences in the muscle activation of RA or EO between the paretic RA (73.97(27.65) µV, EO (69.9(13.0) µV and control RA (52.44(6.16) µV, p=0.46), EO (97.46(25.7) µV, p=0.36) groups. However, during the hip flexion task the muscle activation level of RA in the hemiparetic group was higher (p=0.031) than the control group (hemiparetic group (59(31)% of MVIC), control group (32(11)% of MVIC)	Shapiro-Wilk, t-test, MANOVA Tukey's post-hoc test	Hemiparetic subjects showed increased RA and muscle activity during hip flexion task
Pereira (Brazil 2011) EMG [223]	RA and EO muscle activation and association with hemiparesis	RA muscle activation was higher on the paretic side during leg elevation (p=0.035, Cohen's d=0.94), during lower trunk rotation (p=0.017 d=0.85) and during non-paretic side trunk rotation (p=0.005, d=1.22). EO muscle activation was higher on the non-paretic side during trunk flexion (p=0.019, d=0.75)	t-test, Mann-Whitney test, Shapiro-Wilk test, Wilcoxon test, MANOVA, Box M test, f test, Tukey's post-hoc test	Hemiparetic subjects showed increased RA muscle activity during leg elevation, lower trunk rotation and contralateral trunk rotation. EO activation was higher on non-paretic side during trunk flexion

RA, Rectus abdominis; EO, External oblique; SI, symmetry index;

3.5 Discussion

This systematic review provides a comprehensive assessment of the current literature investigating trunk muscles in older people. Overall, the evidence base has significant limitations, but the available data highlight four key points. Firstly, measurement of stored images of abdominal and MF muscles of older adults can be performed with moderate to substantial reliability using various imaging modalities. Secondly, ageing and possibly decreased physical activity appear to have detrimental effects on the morphology of abdominal and MF muscles. Thirdly, a variety of spinal conditions adversely affect the activation and morphology of MF but LBP appears to mainly affect MA, which in turn affects physical function. Lastly, the effects of stroke on the abdominal and MF muscles and implications for physical function and rehabilitation have not been established.

Consistent evidence was found that measurement of CT, MRI or USI images of older adults' abdominal and MF muscles can be performed with moderate to substantial reliability. Studies of USI test-retest reliability were lacking during the timeframe of our search, but subsequent studies have reported "good-to-excellent" test-retest reliability for muscle thickness at L4-L5 of older adults with and without LBP [247, 248]. Thus, overall, current data are consistent with previous reports of reliability of measurements of younger adults, especially for USI [177], and support the use of these modalities in both research and clinical settings. Conversely, until the reliability of EMG in older adults is assessed, this modality is of unknown utility.

The differences in thickness of abdominal muscles in older compared to younger adults reported in this review (36% - 48% between 20-86 years and 38% - 47% between 21-80 years, excluding TrA in both cases) [186, 244] are consistent with previously reported estimates of decreases in upper and lower limb muscle CSA with age of 1% per year after age 50 years and in muscle mass of 30% between the ages of 20 and 80 years [48]. The absence of age-related differences in TrA and MF muscles [122, 186, 244] may be due to their tonic activation and spinal stabilising role, which require them to be active at low levels when in upright positions to counteract the effects of gravity and postural changes during most activities of daily living [132]. In contrast, the more superficial muscles, which have a greater role in torque generation may be influenced by lifestyle factors or clinical and sub-clinical disease. Strategies to maintain trunk muscles may need to be tailored to different muscles.

The potential influence of physical activity on abdominal and MF muscles has been

demonstrated in the extreme case of chronically bedridden nursing home residents [186], studies of healthier older adults [181] and in studies of subjects during prolonged bed rest [249] but not in the thickness of RA in endurance vs untrained men [243]. The latter were a small group of relatively active older men (for example undertaking hill walking and golf) which could explain this lack of difference. Overall, the results suggest that physical activity plays an important role in maintaining the size and quality of the abdominal and MF muscle of older adults. These findings have clinical significance because physical activity decreases with ageing and older adults are more likely to undergo periods of bed rest due to injury or illness [18]. Future research investigating the effects of maintaining physical activity in older adults and rehabilitation of trunk muscles after prolonged bed rest is needed. There is also a significant evidence gap on the role of trunk muscles in maintaining long-term physical functioning of older adults.

There was limited, but consistent evidence for an adverse effect of various spinal conditions on activation, attenuation and CSA of the MF muscle [183, 184, 228, 238, 239]. Clinically, this suggests that motor control and other rehabilitation programs used by physiotherapists to target MF muscles may also be useful for older adults affected by spinal conditions. It is less clear if this is also the case for non-specific LBP, though longitudinal data [145] do suggest deterioration in the quality of the MF muscle in the presence of LBP. Furthermore, there was a significant longitudinal association between abdominal and paraspinal MA and greater physical function deficits, with stronger associations seen for participants with moderate-extreme LBP, but with no associations with muscle size. It may be that muscle quality rather than quantity is important functionally in older adults. Although strength and endurance exercise programs specifically targeting trunk muscles have been devised [222, 250], their effectiveness for reducing intramuscular fat accumulation and improving muscle quality is not established. Future studies investigating this could lead to improved exercise programs for improving physical capacity of older adults, especially those with LBP.

Reports of abdominal muscle activation from studies of patients after stroke were conflicting. This may be due to the diversity of EMG measures used, the diversity of clinical presentations associated with stroke and movements tested. As we report, reliability of EMG measures in the elderly has not been reported and if low could also contribute to the conflicts between studies. It is possible that addressing trunk muscle function may have clinical relevance for rehabilitation but substantial further research is required. In particular, the lack of investigation of the effects of stroke on abdominal and MF muscle size and quality is an evidence gap that requires further research if we are to understand what role, if any, these muscles have in stroke rehabilitation.

3.6 Limitations

We were unable to undertake meta-analysis because the studies were too heterogeneous to pool. However, we performed a systematic review with a best evidence synthesis to maximise the robustness. Not all studies clearly separated age groups when reporting [122], so there has been some minor mixing of data for adults younger than 50 years. Many studies were small (64% had ≤40 participants) and only one was a longitudinal study, which limits the strength of evidence for the review findings. The review was limited to muscle outcome measures assessed with EMG or imaging and does not address the full spectrum of procedures in which muscle structure and function can be assessed.

3.7 Conclusion

Overall, the evidence examining EMG and imaging measures of trunk muscles in older people has significant limitations, and the role of physiotherapy interventions aimed at these muscles remains unclear. The results suggest areas in which further research could lead to clinically useful outcomes. These include determining the role of the trunk muscles in the physical function of healthy older adults and in those with disease, in particular stroke; developing and testing rehabilitation programs for older people with spinal conditions and LBP; identifying modifiable factors that could mitigate age-related changes, including physical activity and testing whether exercise programs can reduce intramuscular fat accumulation in trunk muscle of older adults.

3.8 Author contributions:

Study conception and design:	TMW, GJ, JAH
Project management of study during implementation:	TMW
Acquisition of data:	WAC, AW, TMW
Design of data analysis plan:	WAC, CLB, TMW
Analysis and interpretation of data:	WAC, AW, JAH, CLB, MLC, PO, TMW
Drafting and revisions of manuscript:	WAC, AW, JAH, CLB, MLC, PO, GJ, TMW

All authors critically reviewed and edited the manuscript, read and approved the final version.

Note: It was not possible to register this systematic review in PROSPERO because registration was sought after it had progressed beyond the point of completion of data extraction and therefore, was not eligible for inclusion in their registry. The letter of rejection from PROSPERO (Appendix 16) was submitted to the journal together with the manuscript, as proof of intent to register the review.

3.9 The assessment of abdominal and multifidus muscles and their role in physical function in older adults: a systematic review - update

3.9.1 Update to April 2018

This section summarises additional relevant studies published since the search date of the systematic review (May 2013) and discusses how these additional data relate to our systematic review findings and contribute further to our understanding of trunk muscles in older adults. For ease of comparison, the studies have been grouped in the same categories as in the published review, i.e. measures of reliability, studies of healthy older adults, studies of participants with spinal conditions, studies of participants with low back pain and other studies. There is no update on studies of participants after stroke as no new studies in this area appear to have been published.

3.9.2 Measures of reliability

The evidence from the systematic review suggested that measurements of abdominal and MF muscles of older adults can be made with moderate to substantial reliability, using CT, MRI and USI. It also identified some key gaps including the lack of studies of USI test-retest reliability, the lack of studies reporting the reliability of abdominal and MF muscle measurements using EMG and the lack of studies reporting the validity of abdominal and MF muscle measurement using any modality. For this update, studies reporting reliability and validity of measurements of abdominal and MF muscles using imaging modalities were grouped by assessment method: CT, MRI and USI and are summarised in Table 3.7.

Among the studies in this update, estimates of reliability of abdominal and multifidus muscle measurements of CSA and attenuation from CT images ranged from moderate to substantial (ICC = 0.78-0.99) [251-255], and coefficient of variation were 0.2% for CSA and 0.4% for muscle attenuation [256]. Similarly, estimates of reliability for measures of MF muscle CSA and attenuation from MRI images ranged from moderate to substantial (ICC = 0.78-0.99) [257-262] and intra-observer correlation for MF CSA measurements was Pearson's r=0.612 [263]. The results from these studies support the findings of our systematic review and provide further support for our findings of consistent evidence that in older adults, assessment of MF muscle size and attenuation using CT and MRI can be accomplished with moderate to substantial reliability.

Studies investigating the reliability of abdominal and multifidus muscle measurements using USI included participants with and without LBP and assessed reliability for both experienced and novice operators. The estimates of reliability ranged from fair to substantial (ICC 0.55 – 0.98) [247, 248, 264-266] (Table 3.7). An evidence gap identified in the systematic review was the lack of test-retest reliability studies for measurements of trunk muscles in older adults. Since 2013, four new studies have been published reporting fair to substantial ICCs for test-retest reliability for the measurement of abdominal and MF muscles of older adults at different spinal levels, using USI. In three of these studies, estimates of reliability for measurements of MF muscle thickness at the L4/L5 spinal level range from moderate to substantial (ICC 0.69 – 0.99) [247, 248, 265] and moderate to substantial (ICC = 0.70-0.98) for the measurement of the transversus abdominis muscle [265]. The fourth test-retest reliability study is part of this thesis and is described in full in chapter 5. This study was in older people with knee osteoarthritis and uniquely provided a comprehensive assessment of intra-observer test-retest reliability for measurement of the rectus abdominis, transversus abdominis, internal oblique and external oblique muscles and MF thickness at spinal levels L2-L5, as well as CSA of MF at spinal levels L2-L5. Reliability was substantial (ICC > 0.81) for all measures except for intra-observer test-retest reliability for the measurement of MF muscle thickness at spinal levels L2-L5, which was fair to substantial (ICC = 0.55-0.86) [264]. Overall, the findings of these studies are in line with the systematic review and extend the evidence for reliability of measurements of abdominal and MF muscles using USI to people with LBP. They also show that measurements of abdominal and MF muscles can be reliably performed by a novice operator.

Another important evidence gap highlighted in the systematic review was the lack of validity studies for any modality of muscle measurements of older people. This has been addressed in a single study, in which criterion validity of USI compared with MRI, for the assessment of MF CSA at the L4 spinal level was evaluated in 20 adults aged 60-85 years with and without chronic LBP [267]. Agreement between USI and MRI was substantial (ICC=0.90-0.97) for the assessment of single images of participants with LBP and for the average measure of 3 images in both participants with and without LBP (ICC= 0.95-0.99). Agreement was lower for single images of participants without LBP (ICC= 0.48-0.86) [267]. The findings from this study complement those of the systematic review and other studies in this update, supporting the use of USI as a valid and reliable tool for the assessment of abdominal and MF muscles of older adults in research and clinical practice.

Table 3.7 Systematic review update - Studies reporting reliability

Author	Number of participants reliability	Age (years)	Sex	Ethnicity	Study setting and health status	Assessment Modality	Measurements tested	Reliability Coefficients	Reliability Type
Abbas et al. 2016 [251]	20	44-99	M=170 F=175	Israeli	NS Spinal Stenosis	CT	CSA, attenuation, MF taken at L3	CSA ICC=0.94 ICC=0.92 Attenuation ICC=0.92 ICC=0.90	Intra-observer Inter-observer
Hyun et al. 2016 [253]	40	61.5	M=2 F=38	NS	NS Degenerative lumbar kyphosis	CT and MRI	CSA, attenuation, MF taken at L1-L5	ICC=0.91, 0.89 ICC=0.78, 0.65	Intra-observer inter-observer
Banno et al. 2017 [252]	100	71.3	F=147	Japanese	Hospital Adult spinal deformity	CT	CSA, MF taken at L4/L5	ICC=0.85 ICC=0.82	Intra-observer inter-observer
Kang et al. 2016 [256]	NS	40->70	M=259 F=264	Korean	Hospital Healthy adults	CT	Attenuation, MF, abdominals taken at L4	CSA CV=0.2% Attenuation CV=0.4%	NS
Katzman et al. 2014 [255]	NS	74.2	M=475	NS	Medical centre records Kyphosis	CT	Attenuation, abdominals taken at L4/L5	ICC ≥ 0.98 ICC ≥ 0.96	Intra-observer inter-observer
Kalichman et al. 2016 [254]	20	M=61.7 F= 59.5	NS	NS	Medical centre records Healthy adults	CT	Attenuation, MF taken at L4/L5	ICC=0.96-0.99 ICC=0.95-0.99	Intra-observer Inter-observer

Author	Number of participants reliability	Age (years)	Sex	Ethnicity	Study setting and health status	Assessment Modality	Measurements tested	Reliability Coefficients	Reliability Type
Farshad et al. 2014 [263]	79	22-80	M=53 F=26	Swiss	Hospital records Lumbar radiculopathy	MRI	CSA, MF taken at level of nerve compression and level below	r=0.612	Inter-observer correlation
Gellhorn et al. 2017 [258]	NS	67	M=101 F=108	African-American White Other	NS Spinal stenosis	MRI	CSA, MF taken at L5	ICC=0.92	Inter-observer
Sasaki et al. 2017 [261]	80	63.1	M=241 F=555	Japanese	Hospital Healthy adults	MRI	CSA, attenuation random images taken from T12-L5	ICC=0.99 ICC=0.99	Intra-observer Inter-observer
Sions et al. 2016 [262]	13	69.3	M=7 F=6	NS	NS LBP	MRI	CSA, attenuation MF taken at L2-L5	CSA and Attenuation ICC= 0.77-.099 ICC= 0.76-.098	Intra-observer Inter-observer
Fortin 2017 [257]	30	18-60	M=19 F=11	NS	NS Disc herniation or spinal stenosis or LBP	MRI	CSA, MF taken at L4-S1	ICC=0.97-1.00 ICC=0.96-0.99	Intra-observer Inter-method
Ni Mhuiris et al. 2016 [259]	10	44-60.8	M=7 F=3	Chinese	University lab Disc degeneration	MRI	Attenuation, MF taken L1-L5	ICC= 0.61-0.91 ICC= 0.33-0.89	Intra-observer Inter-observer

Author	Number of participants reliability	Age (years)	Sex	Ethnicity	Study setting and health status	Assessment Modality	Measurements tested	Reliability Coefficients	Reliability Type
Wilson et al. 2016 [266]	92	60-86	M=57 F=35	NS	University lab Healthy adults	USI	Thickness, CSA, abdominals, MF taken at L2-L5	Abdominals ICC ≥ 0.90 ICC ≥ 0.97 MF ICC ≥ 0.96 ICC ≥ 0.86	Intra-observer Inter-observer
Djordjevic et al. 2014 [265]	98	47	M=54 F=44	NS	University lab Healthy adults	USI	Thickness, TrA, MF taken at L4/L5	ICC=0.93-1.00 ICC=0.61-0.96	Test-retest Intra-observer Inter-observer
Sions et al. 2014 [247]	30	60-85	M=8 F=22	NS	University lab Chronic LBP	USI	Thickness MF taken at L4/L5	ICC=0.90-0.92 ICC=0.98	Test-retest Intra-observer Inter-observer
Sions et al. 2014 [248]	31	60-85	M=16 F=15	White=29 NS=2	University lab Chronic LBP	USI	Thickness MF taken at L4/L5	ICC=0.90-0.93 ICC=0.97-0.98	Test-retest Intra-observer Inter-observer
Cuellar et al. 2017 [264]	23	50-79	M=16 F=7	NS	University lab Healthy adults with knee osteoarthritis	USI	Thickness, CSA, abdominals, MF taken at L2-L5	Abdominals ICC=0.75-0.98 Multifidus ICC= 0.55-0.91	Test-retest Intra-observer
Sions et al. 2017 [267]	20	60-85	M=5 F=15	NS	University lab With and without LBP	USI MRI	CSA MF taken at L4	ICC= 0.95-0.99	Validity agreement

3.9.3 Evidence in healthy older adults

Evidence from the systematic review highlighted an age-related decrease in abdominal muscle thickness ranging from 36% to 48% between the age of 20 and 86 years. In this update, two studies provide further evidence that ageing has a detrimental effect on the morphology of the trunk muscles. In a cross-sectional study of 796 Japanese community-dwelling adults with and without LBP, with a mean age of 63.1 years, Sasaki et al. [261] used MRI to assess paraspinal muscle fat infiltrations and CSA. In this study, men had significantly larger MF muscle CSA than women at all lumbar spinal levels and older age was associated with smaller MF CSA and greater fat infiltrations, with a larger effect size in participants with LBP. Similarly, a 15-year study of 99 monozygotic twins (aged 62.3 at follow up) [268] described decreases in MF muscle CSA at L3-L4 and L5-S1 spinal levels and statistically significant age-related increase in MF fat infiltrations at both spinal levels. The data in these two studies support the finding in the systematic review and importantly, add valuable longitudinal data to the evidence base for detrimental effects of age on abdominal and MF muscles. This information is relevant to clinical practice where strategies to maintain abdominal and MF muscles may be included in rehabilitation programs.

In this update, the evidence for the potential influence of physical activity on abdominal muscles identified in the systematic review has been highlighted and further expanded to the MF muscles. In a study of 281 adults aged 61-71 years, Azuma et al. [167] reported that smaller paraspinal muscle CSA and lower muscle attenuation (increased fat infiltration) were associated with radiographic knee osteoarthritis (RKOA). Also, that females (with or without RKOA) who exercised on a regular basis had greater abdominal muscle CSA and decreased paraspinal muscle fat infiltrations compared with females who did not exercise regularly. Contrary to these findings, decreased maximal walking speed was not associated with MF muscle thickness, in a cross-sectional study of 35 women aged 56-91 years [269]. Fortin et al. [268, 270] reported findings from two separate studies using data from the 15-year longitudinal Twin Spine Study of monozygotic twins. While the 15-year analysis showed no associations between level of physical activity for work or leisure and age-related changes in MF muscle size or composition [268], a separate analysis of the same data reported significant associations between less demanding jobs and increased side to side MF asymmetry at the L3-L4 spinal level, but not the L5-S1 level [270]. Although the evidence for an association between decreased physical activity and MF muscle thickness or composition is not clear, the associations with abdominal muscle size are consistent,

making it relevant to clinical practice as adults tend to decrease their physical activity with increased age and are more likely to endure prolonged periods of bed rest due to illness.
One of the gaps in knowledge identified in the systematic review was the lack of studies assessing associations between trunk muscle measures and measures of physical function in healthy older adults. Results from a study of 174 community-dwelling adults, with a mean age of 82 years [271], indicated that increased abdominal and paraspinal muscle size was associated with increased incidence of falls as well as increased anterior-posterior (AP) motion and velocity and increased mediolateral (ML) motion, which are indicative of decreased balance and increased risk of falls. Plausible explanations for these results may be that trunk muscles size is only partially representative of muscle strength, or that greater weight is associated with both decreased balance and increased muscle size [271]. Another important finding from this study was that decreased abdominal and paraspinal muscle fat infiltrations were associated with decreased incidence of falls and decreased AP and ML velocity and motion [271]. These results seem to indicate that trunk muscle attenuation may be a more important aspect than muscle size for balance.
Finally, the evidence from EMG based studies in this update appear to be as conflicting as those described in the systematic review. In a study of 49 adults with a mean age 78.2 [272], there were significant associations between trunk muscle extension strength and muscle attenuation and electrical impedance myography, independent of muscle size. This was a small pilot study with small effect sizes that limited the clinical relevance of the findings. In another study investigating the effect of a 4-week balance exercise program on static balance of 16 women with a mean age 46.9 years [273], there was a significant decrease in EMG activity in the RA, but not in other abdominal or back muscles examined, despite overall improvements in balance [273].

3.9.4 Participants with spinal conditions

In the systematic review there was limited, but consistent evidence for an adverse effect of spinal conditions on the activation, attenuation and CSA of the MF muscles. The studies include in this update provide further evidence for a detrimental effect of spinal conditions such as Lumbar spinal stenosis (LSS), degenerative scoliosis and adult spinal deformity (ASD) on the MF muscles and added new information of the effect of spinal conditions on physical function. In a retrospective study of 62 older adults with unilateral symptoms of LSS, MF muscle infiltrations at the L4/5 spinal level were greater in older patients with LSS and in those with poorer functional performance as measured by the Japanese Orthopaedic Association Score [274].
Similarly, in a small study of 36 patients diagnosed with LSS, mean age 67 years, increased fat

infiltrations, of the MF muscle and decreased CSA of the psoas muscle at the L5 spinal level were associated with lower physical function scores as measured by the Oswestry Disability Index (ODI) [275]. A cross-sectional study that included 180 patients diagnosed with LSS and a similar number of controls, reported findings that were at odds with the previous reports. In this study, patients diagnosed with LSS had decreased fat infiltrations in the MF muscle and increased CSA of the erector spinae muscle at the L3 spinal level compared with controls. Also, increased MF muscle density was associated with developing LSS [251]. As a possible explanation for this discrepancy, it has been proposed that since the symptomatic effects of LSS are more commonly seen at the lower levels of the lumbar spine, the upper levels tend to compensate for the muscle atrophy and increased fat infiltrations seen in the lower lumbar spinal levels [251], but this has not been corroborated.

The systematic review reported 10% to 22% decrease in MF muscle CSA and increased fat infiltrations on the concave side of patient with degenerative lumbar scoliosis (DLS) [184]. The studies in this update expanded the evidence to adult spinal deformity (ASD), a condition that comprises disorders such as scoliosis, kyphosis and spondylolisthesis. In a case-control study of patients with DLS and age and weight-matched controls, Banno et al. [252] reported a negative correlation between age and MF CSA at the L4/L5 spinal level in patients with DLS. Decreased MF CSA was also strongly correlated with increase in lumbar kyphosis and sagittal spinal deformities. Similar to this and consistent with finding from the systematic review, Kim et al. [276] reported asymmetry in MF muscles, with larger MF CSA on the convex side of patients with DLS, independent of the level, direction or magnitude of the deformity. Finally, in a study of 26 adults aged 50-81 years with degenerative spondylolisthesis by Nava-Bringas et al. [277], there was no correlation between MF muscle size, measured by MRI at L3-S1 spinal levels and physical function (measured by the ODI). Overall, the findings from the studies in this update agree with the consistent evidence from the systematic review for a detrimental effect of spinal conditions on the size and composition of the MF muscles. As is the case in LBP, detrimental effects of spinal conditions on the MF size and composition appear to be primarily at the L4/L5 spinal level.

3.9.5 Participants with low back pain

One longitudinal study in the systematic review provided evidence for associations between increased fat infiltrations in the MF muscles of older adults and greater physical dysfunction over 3 years [145]. Studies of patients with LBP in this update provide further support for an association between increased MF fat infiltrations and decreased physical function in patients

with moderate to severe LBP [146]. They also support findings of increased MF fat infiltrations with increased age in healthy adults and patients with spinal conditions [278-281]. These studies have expanded the evidence to indicate that LBP prevalence and severity is greater in older adults, particularly in women [278, 279].

Resembling the findings in the systematic review, the results of the studies in this update were inconsistent. A 15-year longitudinal study of 99 twins revealed that increased age was not significantly associated with frequency or intensity change in LBP at 1-year follow-up, and instead, there was an association between increased age and decrease LBP frequency at the 15-year follow-up [282]. Although the longitudinal findings regarding MF CSA asymmetry and MF fat infiltrations in this study were inconsistent between L3-L4 and L5-S1 spinal levels, the overall findings are consistent with cross-sectional studies indicating that independent of the duration of LBP symptoms, there were no statistically significant differences in MF CSA or fat infiltrations between the affected and non-effected sides [281, 283], and that neither MF CSA nor size ratio were associated with severity or duration of LBP or nerve root compression [263]. The inconsistency of findings from the studies in this update is similar to the findings in the systematic review, making it difficult to determine the clinical relevance of findings such as MF muscle CSA asymmetry and increased fatty infiltrations when designing rehabilitation programs for older adults with LBP.

3.9.6 Other studies

In the systematic review, there were a small number of studies that did not fit into the previously described categories and were grouped into the "other studies" category. Similarly, in this update, there are several studies grouped under this category. Studies of patients with Parkinson's disease (PD) and camptocormia (abnormal thoracolumbar spinal flexion >30º when standing or walking that disappears in a resting position) in which paravertebral muscles were assessed by MRI, reported increased intramuscular fatty degeneration of the paravertebral muscles in the chronic stage [284], with non-neuropathic-related atrophy of paraspinal muscles with fatty infiltrations on the side of parkinsonian symptom onset [285]. Also, among these patients, there was increased paraspinal muscle activity [286] and an increase in muscle activation among those patients who had sustained falls in the 12-months prior to the study, independent of medication use and severity of symptoms [287], indicating that more motor units are needed to be activated to counteract gravitational forces due to changes in posture due to PD.

The final three studies in this group described individual findings from small studies in patients

with facioscapulohumeral muscular dystrophy, multiple sclerosis and transtibial amputations. A study of ten patients with facioscapulohumeral muscular dystrophy and who were frequent fallers, reported negative associations between abdominal fat infiltrations and posture instability and balance, highlighting a possible important role of abdominal muscles on balance among these patients [288]. In a study of 15 people with multiple sclerosis (MS) and 15 healthy controls, Freund et al. [289] reported no statistically significant differences in abdominal or MF muscle size at rest or change in thickness with contraction between people with MS and control subjects, as measured with USI. Also, there were no significant correlations between muscle contraction ratios and measures of gait or balance in people with MS, and the results from flexion and extension endurance were mixed. The clinical implications of this study are not clear, particularly from such a small number of participants for a condition in which patients can present with a wide variety of symptoms. Finally, an increased muscle activation demand on muscles of the trunk during step ascend and descend exercises in patients with unilateral transtibial amputations was described in a study by Gaffney et al. [290]. This last finding is perhaps not unexpected as some of the main functions of the muscles of the trunk is to transmit forces between upper and lower limb and to provide posture stability during upright activities which would require increased muscle activation to compensate for the asymmetrical trunk muscle movement of these patients.

In conclusion, the studies in this update have strengthened the findings from the systematic review. Significantly, these studies have filled important gaps in the literature that were previously identified, by exploring validity and reliability of abdominal and MF muscle measures at various spinal levels, longitudinal effects of age on muscles of the trunk and associations between muscle of the trunk and physical function. Further evidence was presented highlighting that imaging modalities are reliable tools for the assessment of abdominal and MF muscles of older adults, particularly ultrasound imaging which was shown to be a valid tool for the assessment of these muscles when compared with MRI. the results from this group of studies add support to the findings in the systematic review of evidence for an age-related decrease in trunk muscle size and increase in fat infiltrations. Complementing the findings of the systematic review, the studies of participants with spinal conditions provide consistent evidence for a detrimental effect of these conditions on the abdominal and MF muscles. The evidence from studies of participants with LBP remains inconsistent for older people, making it difficult to interpret their relevance to clinical practice. Finally, the evidence for a detrimental effect of increased fat infiltrations in abdominal and MF muscles appears to be consistent throughout the studies, although more so for the MF muscle at the L4-L5 spinal level.

CHAPTER 4 - METHODOLOGY

4.1 Prelude

Three chapters of this thesis utilised data from an ultrasound imaging (USI) sub-study of the Vitamin D Effect on Osteoarthritis (VIDEO) clinical trial. This chapter provides a general overview of the study population and design of the VIDEO as well as the measures from the VIDEO study and the ultrasound imaging sub-study that were used in chapters 5 to 7 (Table 4.1). Further detail of other factors is included in the methodology section of each chapter.

4.2 VIDEO study population and design

The Vitamin D Effect on Osteoarthritis (VIDEO) study was a randomised, placebo-controlled and double-blind clinical trial, conducted with the main objectives of determining if vitamin D supplementation could reduce knee cartilage volume loss, prevent progression of knee structural abnormalities, improve lower limb muscle strength, and alter the progression of knee pain. The protocol for VIDEO, including its pre-specified analyses, has been published (Appendix 1) [221].

The inclusion criteria were:

- adults aged 50 – 79 years
- ongoing symptoms of knee osteoarthritis for at least six months
- pain levels between 20-80 mm on a 100 mm visual analogue scale (VAS)
- serum 25(OH)D levels between 12.5 and <60 nmol/L.
- Meeting the American College of Rheumatology (ACR) criteria for symptomatic knee OA assessed by a rheumatologist
- ACR functional class rating I, II and III
- relatively good health as indicated by a score of 0 – 2 on a 5-point Likert scale, were zero indicates good health 5 indicates very poor health
- able to read and speak English
- able to understand what the study required and willing to comply with the study instructions

The exclusion criteria were:

- severe radiographic knee osteoarthritis, grade 3 according to Altman's atlas [291]
- severe pain on standing (more than 80 mm on 100-mm VAS)
- any contraindications to having MRI scans

- rheumatoid or psoriatic arthritis, lupus or cancer
- severe cardiac or renal impairment
- hypersensitivity to vitamin D
- any condition affecting oral drug absorption (for example, gastrectomy or malabsorption syndromes)
- significant trauma to knees, including arthroscopy or significant injury to ligaments or menisci of the knee within one year preceding the study
- anticipated need for knee or hip surgery within the next two years
- history of taking vitamin D supplements within the previous 30 days
- history of taking an investigational drug within the previous 30 days [221]

Participants were recruited in Tasmania and Victoria between June 2010 and December 2011 through advertisements in the local media and community groups, and referrals from general practitioners, specialist rheumatologists and orthopaedic surgeons. Participants were randomly assigned to a vitamin D or a placebo group using computer-generated allocation in a 1:1 ratio. Participants, researchers and study administrators were blinded to treatment allocation until all data were collected, cleaned and statistical analyses for primary outcomes and the data for this thesis were completed.

4.3 25-Hydroxyvitamin D Assays

Serum25-hydroxyvitamin D was assayed as per the clinical trial protocol, at screening, 3 months, and 24 months using direct competitive chemiluminescent immunoassays (DiaSorin Inc). The intraassay and interassay coefficients of variation were 3.2% and 6.0% [292].

4.4 Intervention

Participants in the treatment group were asked to take one 50,000 IU vitamin D3 (cholecalciferol) capsule per month, for 24 months. Participants in the control group were given an identical inert placebo. The vitamin D3 capsules and inert placebo were acquired from Nationwide Compounding Pharmacy, Melbourne, Australia [221].

4.5 Ethics

The clinical trial received ethics approval from The Tasmanian Health and Human Medical Research Ethics Committee (reference number H1040) and Monash University Human Research

Ethics Committee (reference number CF10/1182 - 2010000616). Informed written consent was obtained from all participants.

The photographs of muscles in the first chapter were taken during various stages of dissections performed by Derek Choi-Lundberg and William Cuellar, during the development of audio-visual resources for medical students at the school of medicine, College of Health, University of Tasmania. The bodies were kindly donated by community members to the Body Bequest Program at the school of medicine. All donors signed informed written consent for their bodies to be used for medical education and research (Appendix 14). The reproduction of the photographs for this thesis received ethics approval from The Tasmanian Health and Human Medical Research Ethics Committee (reference number H0017462) (Appendix 15)

4.6 Ultrasound imaging sub-study

The studies reported in chapters 5 to 7 of this thesis originated from a USI sub-study of the VIDEO clinical trial that was undertaken at the Hobart site. Data from this sub-study were used to investigate the test-retest reliability of abdominal and multifidus measurements using ultrasound imaging (chapter 5) and the effect of 12 months of vitamin D supplementation on the size of the abdominal and multifidus muscles (chapter 6). The latter was a secondary analysis of the VIDEO clinical trial. Finally, these data were also used to investigate the associations between abdominal and multifidus muscle size and physical activity, physical function and quality of life (chapter 7). This sub-study received ethics approval from The Tasmania Health and Human Medical Research Ethics Committee (reference number H1040) as part of the main VIDEO ethics application. Informed written consent was obtained from all participants.

4.7 Outcome measures

Measurements from ultrasound images of abdominal and multifidus muscle thickness and cross-sectional area were outcome factors for the studies reported in chapter 5 and 6 and the study factor for the analysis reported in chapter 7. Methods of capture and measurements are described in detail in chapter 5, under 5.3.2 “Image capture and measurement” of the methods section [264] and brief descriptions of the process are included in chapters 6 and 7 in the methods sections.

4.8 Measures of physical activity, physical function and quality of life

Measures of physical activity were assessed by the short version of the International Physical

Activity Questionnaire (IPAQ) [293] (Appendix 2). Ambulatory physical activity was measured using Yamax Digi-Walker SW-200 pedometers that recorded total daily steps for 7 days. Deficits in physical function were assessed by the functional deficit subscale of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) (Appendix 3) [294]. Quality of life was assessed by the Assessment of Quality of Life instrument *(*AQoL) (Appendix 4) [295]. Detailed descriptions of these instruments are included in the methods section in chapter 7.

4.9 Other measures

Each participant's body weight was measured using calibrated scales (Heine S-7307, Heine, New Hampshire, USA). Height was measured by stadiometer to the nearest 0.1 cm (Leicester Height Measure, Invicta Plastics Ltd, Leicester, UK). Body mass index (BMI) was calculated as weight (kg)/height (m^2).

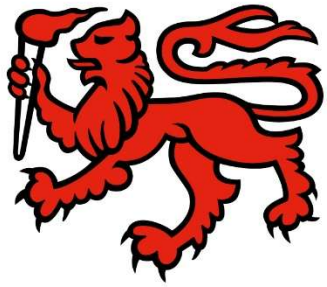
Current low back pain status was assessed by a questionnaire that included the question "Do you currently have any pain in your back?" Pain scores were obtained using a Visual Analogue Scale (0-100 mm) with zero indicating no pain and 100 the worst pain the participant had ever had (Appendix 5). History of back surgery, abdominal surgery and medication use were obtained by questionnaire (Appendix 6).

Leg strength measures to the nearest kilogram were obtained for both legs simultaneously using a dynamometer (TTM Muscular Meter, Tokyo, Japan) as described by Scott, 2009a [296]. This is an isometric strength muscle test, predominantly for the quadriceps and hip extensor muscles. Hand grip strength was assessed to the nearest kg using a hydraulic hand dynamometer (Saehan Corporation, Masan, Korea) (Appendix 6).

4.10 Statistical analysis

The statistical methods used in this research are described in detail in the corresponding chapters. Statistical significance was set at a two-tailed p-value ≤ 0.05. All statistical analyses were performed using STATA 12 and 14 for Windows (StataCorp, College Station TX, USA).

CHAPTER 5 - TEST-RETEST RELIABILITY OF MEASUREMENTS OF ABDOMINAL AND MULTIFIDUS MUSCLES USING ULTRASOUND IMAGING IN ADULTS AGED 50 TO 79 YEARS



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(Original article included as Appendix 12)

5.1 Prelude

Chapter 1 gives a brief overview of the reliability of EMG and imaging methods used to assess muscles of the trunk. The validity and reliability of measurements of abdominal and MF muscles using USI are well established in young people, but this may differ in older people for several reasons, including morphological features of ageing muscle, which increase the difficulty of assessing these muscles. The systematic review in chapter 3 provided a synthesis of the current literature on the assessment of abdominal and MF muscles and reported that in older adults, there were gaps in knowledge regarding validity and test-retest reliability of measurements of these muscles using USI.

Thus, this study aimed to evaluate the test-retest reliability of USI for assessing abdominal and MF muscle thickness and MF CSA at the L2–L5 vertebral levels. It should be noted that apart from the numbering of tables and figures that were changed to follow the thesis sequence, the text in this chapter is presented as published in The Journal of Musculoskeletal Science and Practice; Cuellar WA, Blizzard L, Callisaya ML, Hides JA, Jones G, Ding C, et al. Test-retest reliability of measurements of abdominal and multifidus muscles using ultrasound imaging in adults aged 50-79 years. Musculoskelet Sci Pract. 2017;28(e1-e88):79-84 [264]. This journal has an impact factor of 2.12 and the paper has been cited 2 times.

5.2 Introduction

The muscles of the lumbopelvic region have a role in stability and function of the spine, locomotion and maintenance of posture and balance [6, 9]. However, research on abdominal and lumbar multifidus (MF) muscles in older adults is limited [138].

Ultrasound imaging (USI) is used clinically and in research to assess muscle morphology. Its reliability in older adults is not yet fully ascertained. There are two key aspects of reliability, namely reliability of repeatedly measuring the same image and test-retest reliability, where the entire imaging process is repeated by the same person days or weeks apart and measurements made on the resulting sets of images [297]. Test-retest reliability is critical to clinical practice and longitudinal research where imaging is repeated to monitor patients' progress. This has greater potential for measurement error than just remeasuring the same image due to additional sources of variation, for example, from repositioning the participant and transducer and identification of landmarks [298].

The inter and intra-rater reliability of repeatedly measuring ultrasound images of abdominal and multifidus muscles has recently been reported as substantial in adults aged 65 to 89 years [266], consistent with that in lateral abdominals in adults of mean age 72 years [245]. However, despite the critical importance of test-retest reliability to clinical and research practice, in older adults this has only been reported for MF thickness at the L4-L5 spinal level [247, 248] [138] and not for MF cross-sectional area (CSA) or abdominal muscle thickness. Test-retest reliability of MF thickness beyond L4-5 is important as MF morphology varies by spinal level [162] and clinical conditions such as low back pain (LBP) affect MF at levels additional to L4-5. Therefore, this study aimed to evaluate the test-retest reliability of USI for assessing abdominal and MF muscle thickness and MF CSA at the L2–L5 vertebral levels.

5.3 Methods

5.3.1 Participants

Participants were drawn from an USI sub-study on trunk muscles (n=186) of the "Vitamin D Effect on Knee Osteoarthritis" (VIDEO) clinical trial in Tasmania (n=261) [292]. In brief, VIDEO participants aged 50-79 years, with symptomatic knee osteoarthritis for at least six months, and serum 25-(OH)D levels between 12.5 to 60 nmol/L, were recruited from the community. Twenty-three participants from the USI sub-study took part in the reliability study. The USI sub-study was approved by The Tasmania Health and Human Ethics Committee. All participants gave written informed consent. We measured each participant's height by stadiometer, weight by calibrated scales, calculated body mass index (BMI) (weight (kg)/height (m^2)) and ascertained LBP status by questionnaire asking, "Do you currently have any pain in your lower back?".

5.3.2 Image capture and measurement

USI was performed twice, one week apart, using a Phillips HDI 5000 diagnostic ultrasound (Bothwell, WA, USA) in brightness (B) mode, with a hand-held 4-7 MHz curved array transducer. All USI was conducted by a physiotherapist who undertook 36 hours of practical training in USI from JAH. Single sets of images were obtained to reduce time to accommodate the USI sub-study within the clinical trial.

Transverse images of transversus abdominis (TrA), internal oblique (IO) and external oblique (EO) were obtained at rest and contracted with participants directed to "take a relaxed breath in and out, hold your breath out, and then draw in your lower abdomen without moving your spine"

[298]. Images were obtained along a line halfway between the lower angle of the rib cage and the iliac crest for right, then left, sides. The transducer was oriented transversely such that full vision of all muscle bellies was possible and the fascial insertion of TrA was close to the medial edge of the image with the muscle relaxed. In younger adults, the medial fascial insertion of TrA would be positioned 2 cm from the medial edge of the screen image [298], but this was not possible in these older adults due to body habitus. Transverse images of rectus abdominis (RA) were obtained at rest, for right, then left sides, with the transducer oriented transversely and placed lateral to the umbilicus until RA was centred on the screen [121].

For MF thickness, parasagittal images were obtained on the right side at rest and on isometric contraction at L2-L3 to L5-S1 vertebral levels. For the latter, participants were instructed to take a relaxed breath in and out, hold their breath out and try to slowly "swell" and contract the muscle without moving the spine [174]. Participants lay prone with one pillow under the abdomen to reduce lumbar lordosis. L2 to L5 spinous processes were palpated, marked with a pen and then confirmed using USI [299]. Bilateral CSA images of MF were obtained in the transverse plane at vertebral levels L2 to L5 with the muscles relaxed.

Images were stored and later measured offline by a single examiner using ImageJ software 1.36b (http://imagej.nih.gov/ij/). Abdominal muscle thickness was measured as the perpendicular distance between the superior and inferior muscle fascias at approximately the middle of the image identified using the software's Cartesian coordinates (Figure 5.1A and 5.1B) [298]. MF CSA was measured by tracing the inner edge of the fascial boundaries (Figure 5.1C) [300] and thickness measured from the tip of the zygapophyseal joint to the inferior fascial edge of the superior border of the muscle (Figure 5.1D) [301]

5.3.3 Statistical Analysis:

Percentage thickness change was calculated as 100*(thickness of muscle contracted - thickness relaxed)/thickness relaxed. Bland and Altman plots were inspected to identify any systematic patterns in the differences associated with muscle size [302]. Intraclass correlation coefficients were calculated (ICC 3,1) [303] and classified according to the recommendations of Shrout [226] (≤0.10 = virtually none, 0.11–0.40 = slight, 0.41–0.60 = fair, 0.61–0.80 = moderate, and 0.81–1.0 = substantial). Standard error of measurement (SEM) [304] and minimal detectable change (MDC) were also calculated. STATA 12 was used for data analysis.

5.4 Results:

Table 5.1 summarises the characteristics of the reliability study participants and of the other participants in the USI sub-study of the VIDEO trial. The reliability study group included relatively more males, and women who were shorter and lighter than the other women in the USI sub-study.

Other than for the right IO when contracted (ICC 0.75), ICC values for abdominal muscles were substantial (0.87-0.98) (Table 5.2 and 5.3). Other than for IO when contracted (difference 6.5%), the differences between measurements were relatively small (≤3.2%) and considerably smaller than their corresponding MDC values. ICCs were lower, and SEM values higher, for percentage thickness change. Reliability of measurements of right MF thickness (at rest and contracted) was fair to moderate at the L2-L3 and L3-L4 spinal levels (ICC 0.55-0.74) (Table 5.4) and moderate to substantial at other levels. On average, the test-retest differences were small (≤3%) and considerably smaller than the corresponding MDC. Percentage change thickness was not reliably measured. Reliability of MF CSA measures was substantial (ICC 0.84-0.91) (Table 5.5), with small test-retest differences that were much smaller than the MDC. Bland and Altman plots of all muscle measurements revealed no systematic pattern of variability across the range of measurement (data not shown).

5.5 Discussion

This study reports test-retest reliability of USI and measurement of thickness of abdominal and MF muscles, and MF CSA (L2-L5) in adults aged 50 to 79 years. Importantly, we assessed test-retest reliability for muscles for which this has not previously been reported in older adults [138]. Reliability was substantial for all measures other than thickness of IO and of MF at L2-L3 and L3-L4 spinal levels, supporting the use of USI as a reliable tool for the assessment of abdominal and MF muscle thickness and MF CSA of older adults for clinical and research purposes.

Age related changes in skeletal muscle such as decreased water and increased fat content and fibrous tissue can increase ultrasound image echogenicity and could reduce the reliability of muscle measurements in older adults [122, 185].

Despite this and the additional potential for measurement error during the process of taking repeated ultrasound measures, test-retest reliability of abdominal muscle thickness and MF CSA in our study were substantial (ICC = >0.81), and comparable with the reliability of just

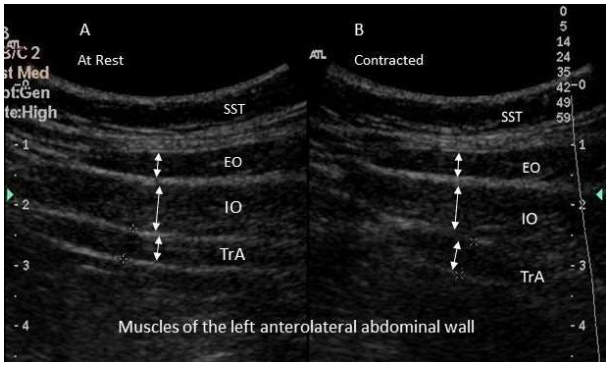
measuring images of the same muscles in a population-based sample of adults aged 65 to 89 years (ICC= > 0.85) [266]. Furthermore, the test-retest reliability of MF CSA was comparable to that of young adults (ICC= 0.72-0.80) [305]. This suggests that USI test-retest assessment of abdominal and MF muscle thickness at rest and contracted, MF CSA at rest and percentage change in abdominal thickness of older adults can be reliably performed by a trained assessor following a standardised protocol.

The test-retest reliability of measurements of MF muscle thickness in our study ranged from fair to substantial (ICC = 0.55-0.86), being somewhat lower at L2-3 and L3-4 spinal levels. This is lower than previously reported for at L4-L5 in older adults [247, 248], which may be in part due to that study using the average of three measurements to calculate ICCs and SEMs. Averaging three measurements improves measurement precision (SEM) by up to 50% [306], but only delivers modest improvements in reliability of MF thickness compared with single measurements [265, 301]. Potential gains in reliability need to be weighed against the logistical disadvantages (e.g. time) of performing multiple measurements in clinical and research settings.

The reasons for the lower reliability of measuring upper spinal segments in our study are not clear. One contributing factor may be the higher degree of difficulty localising these segments and excluding longitudinal muscle fibres from the erector spinae in the measurement of MF thickness. Although the reasons for the marked side-to-side difference in the reliability of thickness and percentage thickness change of the IO are also unclear, our results are consistent with a previous image reading study confined to lateral abdominals in adults of mean age 72 years (Stetts et al (2009). It is possible that consistently imaging the right side first created a learning effect that lessened variability in the contraction of the left IO.

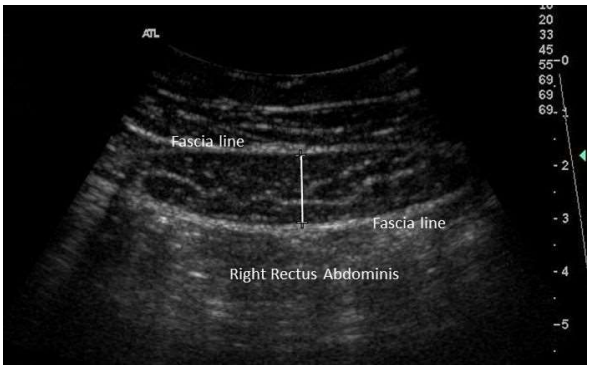
Figure 5.1 Split-screen image showing the muscles of the left anterolateral abdominal wall (A and B) and multifidus thickness and cross-sectional area (C and D)

A



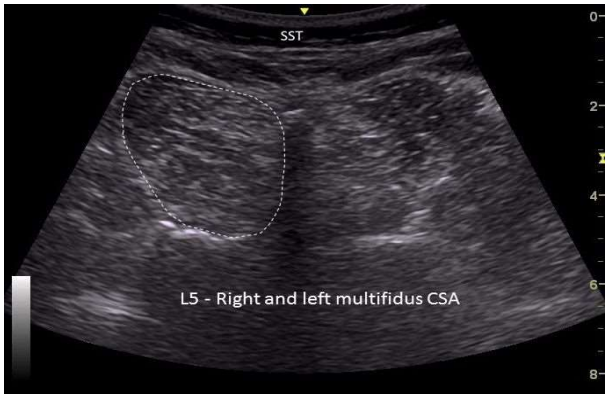
Split-screen image showing the muscles of the left anterolateral abdominal wall at rest (A) and contracted (B). Abbreviations: SST: superficial soft tissue, (EO): external oblique, (IO): internal oblique, (TrA) transversus abdominis.

B



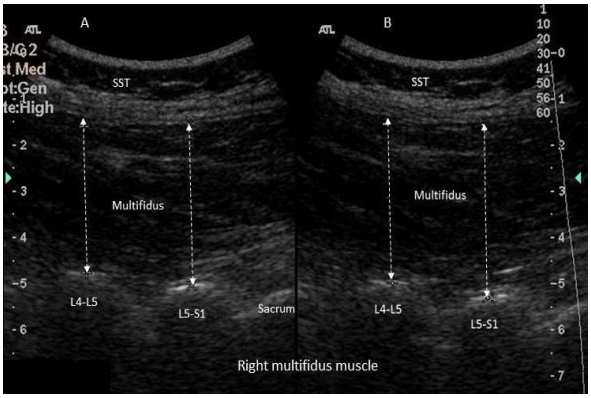
Ultrasound image showing the right rectus abdominis muscle. Thickness of the muscle was measured at rest as the perpendicular distance between the superior and inferior hypoechoic muscle fascias at the middle of the image

C



Bilateral image of multifidus in transverse section at the L5 vertebral level. Cross-sectional area (CSA) of the multifidus muscle was measured by tracing around the inner edge of the fascial boundaries of the muscle as shown on the left side of the image. Abbreviations: SST, sub-cutaneous soft tissue

D



Split-screen parasagittal image of the right multifidus muscle at rest (A) and contracted (B). Thickness measurements were made from the tip of the zygapophyseal joint to the inferior fascial edge of the superior border of the muscle. Abbreviations: SST, sub-cutaneous soft tissue

Table 5.1 Characteristics of participants in the reliability study and of remaining ultrasound sub-study participants (non-participants)

Characteristic	Reliability study (N=23)	Non-participants (N=163)
Age (yrs.)	62.4 (6.3)	64.7 (7.3)
Sex: Males, % (n/N)	70 (16/23)	54 (88/163)
Height (cm) (males, females	177.8(6.1), 158.4(6.6)	176.1(6.5), 161.6(6.1)
Weight (kg) (males, females)	88.4(12.6), 68.5(16.0)	91.8(13.6), 78.4(14.7)
BMI (kg/m^2)	29.7 (11.7)	29.8 (4.8)
Low Back Pain, % (n/N)	39.1 (9/23)	35.6 (58/163)

Results are reported mean (standard deviation) unless otherwise stated. %: percentage; BMI: body mass index

Table 5.2 Test-retest reliability of measuring right abdominal muscle thickness (cm)

		Test	Retest	Difference			Intraclass Correlation	
Muscle	**N**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**SEM**	**MDC_{95}**	**ICC(3,1)**	**95% CI**
RA	23	0.86 (0.19)	0.88 (0.19)	-0.016 (0.061)	0.04	0.12	0.95	(0.88, 0.98)
TrA (rest)	23	0.39 (0.10)	0.40 (0.11)	-0.004 (0.034)	0.02	0.07	0.95	(0.88, 0.98)
TrA (contract)	23	0.58 (0.16)	0.59 (0.16)	0.010 (0.004)	0.04	0.10	0.95	(0.89, 0.98)
Thickness change, %	23	50.66 (32.76)	54.35 (38.03)	-3.689 (21.704)	15.35	42.54	0.81	(0.61, 0.92)
IO (rest)	23	0.73 (0.16)	0.75 (0.17)	-0.024 (0.013)	0.05	0.12	0.92	(0.83, 0.97)
IO (contract)	23	0.95 (0.24)	1.01 (0.28)	-0.062 (0.185)	0.13	0.36	0.75	(0.49, 0.89)
Thickness change, %	23	30.54 (22.65)	35.12 (31.71)	-4.580 (32.967)	23.31	64.61	0.28	(-0.14, 0.62)
EO (rest)	23	0.41 (0.10)	0.41 (0.10)	-0.008 (0.031)	0.02	0.06	0.95	(0.89, 0.98)
EO (contract)	23	0.47 (0.99)	0.49 (0.10)	-0.013 (0.052)	0.04	0.10	0.87	(0.71, 0.94)
Thickness change, %	23	19.34 (21.80)	19.84 (19.89)	-0.5 (15.440)	10.92	30.26	0.73	(0.46, 0.87)

Abbreviations: *RA,* rectus abdominis; *EO,* external oblique; *IO,* internal oblique; *TrA,* transversus abdominis; *rest,* resting thickness (cm); *contract,* contracted thickness (cm); *SD,* standard deviation; *SEM,* standard error of measurement; *MDC,* minimal detectable change; *ICC,* intra-class correlation coefficient (95% confidence interval)

Table 5.3 Test-retest reliability of measuring left abdominal muscle thickness (cm)

		Test	Retest	Difference			Intraclass Correlation	
Muscle	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**SEM**	**MDC_{95}**	**ICC(3,1)**	**95% CI**
RA	23	0.85 (0.18)	0.86 (0.19)	-0.007 (0.036)	0.03	0.07	0.98	(0.96, 0.99)
TrA (rest)	23	0.37 (0.10)	0.38 (0.10)	-0.000 (0.036)	0.03	0.07	0.93	(0.84, 0.97)
TrA (contract)	23	0.60 (0.15)	0.60 (0.16)	-0.003 (0.049)	0.04	0.10	0.95	(0.87, 0.98)
Thickness change, %	23	63.53 (36.04)	61.77 (28.92)	1.762 (17.916)	12.67	35.11	0.85	(0.68, 0.93)
IO (rest)	23	0.77 (0.19)	0.75 (0.20)	0.024 (0.068)	0.05	0.13	0.94	(0.86, 0.97)
IO (contract)	23	1.06 (0.32)	1.03 (0.33)	0.026 (0.086)	0.06	0.17	0.96	(0.92, 0.99)
Thickness change, %	23	37.08 (22.90)	38.36 (27.19)	-1.287 (15.460)	10.93	30.30	0.81	(0.61, 0.92)
EO (rest)	23	0.42 (0.11)	0.42 (0.09)	0.006 (0.040)	0.03	0.08	0.92	(0.82, 0.97)
EO (contract)	23	0.52 (0.14)	0.52 (0.14)	-0.001 (0.043)	0.03	0.09	0.95	(0.89, 0.98)
Thickness change, %	23	24.07 (27.13)	25.55 (28.95)	-1.477 (16.359)	11.57	32.06	0.83	(0.64, 0.92)

Abbreviations: *RA,* rectus abdominis; *EO,* external oblique; *IO,* internal oblique; *TrA,* transversus abdominis; *rest,* resting thickness (cm); *contract,* contracted thickness (cm), *SD,* standard deviation; *SEM,* standard error of measurement; *MDC,* minimal detectable change; *ICC,* intra-class correlation coefficient (95% confidence interval).

Table 5.4 Test-retest reliability of right lumbar multifidus muscle thickness measures (cm)

		Test	Retest	Difference			Intraclass Correlation	
Muscle	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**SEM**	**MDC_{95}**	**ICC(3,1)**	**95% CI**
MF L2-L3 (rest)	23	2.60 (0.30)	2.52 (0.41)	0.078 (0.338)	0.24	0.66	0.55	(0.19, 0.78)
MF L2-L3 (contract)	23	2.83 (0.38)	2.80 (0.43)	0.032 (0.292)	0.21	0.57	0.74	(0.48, 0.88)
Thickness change, %	23	8.95 (10.42)	11.44 (9.20)	-2.491 (11.586)	8.19	22.71	0.30	(-0.11, 0.63)
MF L3-L4 (rest)	23	2.42 (0.33)	2.372(0.32)	0.044 (0.302)	0.21	0.59	0.57	(0.21, 0.79)
MF L3-L4 (contract)	23	2.66 (0.40)	2.61 (0.33)	0.052 (0.315)	0.22	0.62	0.63	(0.31, 0.83)
Thickness change, %	23	10.58 (11.52)	10.55 (10.10)	0.033 (15.896)	11.24	31.16	-0.08	(-0.47, 0.34)
MF L4-L5 (rest)	23	2.85 (0.48)	2.87 (0.60)	-0.027 (0.315)	0.22	0.62	0.83	(0.64, 0.92)
MF L4-L5 (contract)	23	3.02 (0.52)	3.05 (0.65)	-0.031 (0.313)	0.22	0.61	0.86	(0.69, 0.94)
Thickness change, %	23	6.12 (6.89)	6.28 (8.97)	-0.165 (8.546)	6.04	16.75	0.43	(0.03, 0.71)
MF L5-S1 (rest)	23	2.84 (0.37)	2.86 (0.49)	-0.016 (0.311)	0.22	0.61	0.74	(0.48, 0.88)
MF L5-S1 (contract)	23	3.04 (0.47)	3.09 (0.57)	-0.048 (0.413)	0.29	0.80	0.69	(0.39, 0.86)
Thickness change, %	23	6.90 (6.95)	8.46 (11.36)	-1.561 (12.244)	8.66	24	0.16	(-0.27, 0.53)

Abbreviations: *MF,* Multifidus; *L2 - L5,* lumbar vertebral level; *rest,* resting thickness (cm); *contract,* contracted thickness (cm); *SD,* standard deviation; *SEM,* standard error of measurement; *MDC,* minimal detectable change; *ICC,* intra-class correlation coefficient (95% confidence interval)

Table 5.5 Test-retest reliability of lumbar multifidus cross-sectional area measures (cm2)

		Test	Retest	Difference			Intraclass Correlation
Muscle	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**SEM**	**MDC_{95}**	**ICC(3,1) 95% CI**
(R) MF L2	23	2.93 (0.46)	3.01 (0.50)	-0.079 (0.271)	0.19	0.29	0.84 (0.66, 0.93)
(L) MF L2	23	2.90 (0.46)	2.94 (0.49)	-0.039 (0.266)	0.19	0.28	0.84 (0.67, 0.93)
(R) MF L3	23	3.78 (0.53)	3.87 (0.57)	-0.088 (0.252)	0.18	0.22	0.90 (0.77, 0.96)
(L) MF L3	23	3.86 (0.58)	3.79 (0.59)	0.067 (0.259)	0.18	0.22	0.90 (0.78, 0.96)
(R) MF L4	23	4.74 (0.60)	4.79 (0.67)	-0.048 (0.274)	0.19	0.23	0.91 (0.80, 0.96)
(L) MF L4	23	4.84 (0.56)	4.82 (0.62)	0.014 (0.293)	0.21	0.27	0.88 (0.74, 0.95)
(R) MF L5	23	5.31 (0.56)	5.39 (0.60)	-0.085 (0.260)	0.18	0.22	0.90 (0.78, 0.96)
(L) MF L5	23	5.39 (0.57)	5.38 (0.56)	0.008 (0.264)	0.19	0.23	0.89 (0.76, 0.95)

Abbreviations: (R), right side; (L), left side; *MF,* Multifidus; *L2 - L5,* lumbar vertebral level; *SD,* standard deviation; *SEM,* standard error of measurement; *MDC,* minimal detectable change; *ICC,* intra-class correlation coefficient (95% confidence interval)

Estimates of reliability for percent thickness change were low, particularly those for MF (ICC -0.08-0.43), consistent with previous reports for L4-5 MF thickness [247] and IO. This is not unexpected, as multiple factors influence percentage muscle thickness changes such as resting state, contraction type, and variability in performance of the contraction [307]. Therefore, current approaches to assessing percentage thickness change of lumbar MF and IO appear insufficiently reliable to measure changes in muscle size over time. Further research could investigate ways to improve the reliability of these measures, possibly through different approaches to standardising the performance of contractions, and alternative approaches that more closely target IO.

5.6 Study limitations

This study has several limitations. A trained examiner performed USI so the results may not be generalizable to examiners with less training, though MF thickness has been measured with high test-retest reliability in older adults by operators with limited USI training [247]. Reliability may have been higher with multiple rather than single measurements, but the reliability we achieved suggests that single measurements can be made with substantial consistency, at least at the lower spinal levels where LBP is more prevalent. Lastly, participants were vitamin D insufficient and so the muscle measures are not normative for the general population.

5.7 Conclusion

Despite the challenges of imaging older adults using USI, a trained assessor can reliably assess abdominal and MF muscle thickness at rest and contracted, CSA at rest and percentage change in abdominal thickness, but not percentage change in MF thickness, on different days. The substantial reliability of most measures suggest that USI performed by a trained assessor using established protocols is sufficiently reliable to be used in clinical practice and for research in older people.

5.8 Author contributions:

Study conception and design:	TMW, GJ, JAH, CD
Project management of study during implementation:	TMW
Acquisition of data:	WAC
Design of data analysis plan:	WAC, JAH, CLB, TMW
Analysis and interpretation of data:	WAC, JAH, CLB, MLC, TMW
Drafting and revisions of manuscript:	WAC, JAH, CLB, MLC, GJ, TMW, CD

All authors approved the final version of the manuscript.

5.9 Conflicts of Interest and Sources of Funding:

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CHAPTER 6 - VITAMIN D SUPPLEMENTS FOR TRUNK MUSCLE MORPHOLOGY IN OLDER ADULTS: SECONDARY ANALYSIS OF A RANDOMISED CONTROLLED TRIAL

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(Original article included as Appendix 13)

6.1 Prelude

Having established the test-retest reliability of USI for assessing abdominal and lumbar multifidus muscles, allowed us to proceed to use this technique to assess these muscles and use these measures as outcomes factors in a randomised controlled trial design. The third section of the introduction chapter discussed previous research that investigated associations between vitamin D supplementation and measures of muscle function, namely, muscle strength, muscle mass and power. However, only a few studies have been conducted on the effect of vitamin D supplementation on muscle size [309, 310]. In the systematic review in chapter 4, no studies had examined the effect of vitamin D supplementation on muscles of the trunk of older adults. As discussed in the third section of the introductory chapter, the effect of vitamin D supplementation on muscles of the trunk is of particular interest because low vitamin D levels are associated with decreased postural balance and increased risk of falls in older adults [62]. This study aimed to evaluate the effect of 12 months vitamin D supplementation on the size and function of the abdominal and multifidus muscles in a sample of community-dwelling adults aged 50 – 79, with low-level serum 25(OH)D. It should be noted that apart from the numbering of tables and figures that were changed to follow the thesis sequence, the text in this chapter is presented as published in the Journal of Cachexia, Sarcopenia and Muscle. Cuellar WA, Blizzard L, Hides JA, Callisaya ML, Jones G, Cicuttini F, et al. Vitamin D supplements for trunk muscle morphology in older adults: secondary analysis of a randomized controlled trial. Journal of Cachexia, Sarcopenia and Muscle. 2018, DOI: 10.1002/jcsm.12364. This journal has an impact factor of 12.5 and the paper was accepted in late 2018.

6.2 Introduction

Population levels of serum 25-hydroxyvitamin D (25(OH)D) are variable around the world, but deficiency is common in older adults due to decreased sun exposure, decreased production of vitamin D in the skin, insufficient intake of vitamin D in their diet and institutionalisation [188-191]. Mean population 25(OH)D levels commonly fall below 50 nmol/L (20 ng/ml), which is considered to be the minimum target level for adequate bone health, mineral homeostasis and muscle function [191, 193, 200].

Common clinical presentations of severe vitamin D deficiency include bone pain, gait disturbances and muscle weakness, especially of proximal muscles of the upper and lower limbs and muscles of the trunk [213]. Previous research has found that vitamin D plays a vital role in muscle development and growth [209]. The mechanism may be through $1,25(OH)_2$ binding to a

specific vitamin D receptor found in skeletal muscle [54, 210] leading to de novo protein synthesis and thus muscle cell proliferation and growth [59, 211]. Furthermore, a review of randomised controlled trials (RCTs) has examined the effect of vitamin D supplementation on several aspects of muscle function including lower limb strength, handgrip, postural balance, gait speed and physical performance (timed-up-and-go (TUG) test) [311]. Even though evidence in this review was conflicting, 7 of 11 studies demonstrated beneficial effects, as has another published RCT [312]. A more recent systematic review and meta-analysis of 30 RCTs by Beaudart et al. [216] found small but significant positive effects of vitamin D supplementation on lower limb muscle strength, although there were no effects on muscle mass or power. Thus, there is both a biological basis and clinical trial evidence for considering that correcting vitamin D deficiency may improve muscle strength and function.

Muscles of the trunk, particularly the abdominal and lumbar multifidus muscles (MF), are postural muscles tonically active during daily upright activities [186] and essential for the stability of the spine, balance and posture [6, 9, 132]. Trunk muscle size is correlated with strength [272, 313] and among older adults, trunk muscle strength has been found to be associated with mobility and falls [7, 271]. The effect of vitamin D supplementation on muscles of the trunk is of particular interest because low 25(OH)D levels are associated with decreased postural balance [311] and increased risk of falls by older adults [314]. Consequently, vitamin D supplementation has the potential to be a relatively cheap intervention to improve postural muscle function and decrease the risk of falling among older adults. Despite this, to our knowledge, the effects of vitamin D supplementation on trunk muscles has not been assessed previously. Therefore, the objective of this randomised controlled trial was to evaluate the effect of 12-months of vitamin D supplementation compared with placebo, on morphology and function of the trunk muscles of adults aged 50 to 79 years with low serum 25(OH)D levels.

6.3 Methods

6.3.1 Trial design

The Vitamin D Effect on Osteoarthritis (VIDEO) study was a randomised, placebo-controlled and double-blind clinical trial conducted between June 2010 and December 2013, with the main objectives of determining if vitamin D supplementation could reduce knee cartilage volume loss, prevent progression of knee structural abnormalities, improve lower limb muscle strength, and alter the progression of knee pain [221, 292]. The protocol for VIDEO and its pre-specified analyses has been published [221]. This pre-specified secondary analysis investigating the effects of

vitamin D supplementation on the size of abdominal and lumbar multifidus muscles over twelve months was undertaken in one of the two VIDEO sites, namely Hobart, Tasmania, Australia. VIDEO was registered with the Australian New Zealand clinical trial registration agency, ClinicalTrials.gov identifier: NCT01176344; Australian New Zealand Clinical Trials Registry: ACTRN 12610000495022 [221]. The clinical trial and sub-studies were conducted following the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and the 2007 Australian National Statement on Ethical Conduct in Human Research.

6.3.2 Participants

Participants were recruited through advertisements in the local media and community groups, and referrals from general practitioners, specialist rheumatologists and orthopaedic surgeons. Inclusion and exclusion criteria are described in detail in the published clinical trial protocol [221]. In brief, participants were people aged 50-79 years, with ongoing symptoms of knee osteoarthritis for at least six months with pain levels between 20-80 mm on a 100 mm visual analogue scale (VAS), and serum 25(OH)D levels between 12.5 and 60 nmol/L (5.2 to 24 ng/ml). Exclusion criteria included: severe radiographic knee osteoarthritis, severe pain on standing, hypersensitivity to vitamin D, any condition affecting oral drug absorption and anticipated need for knee or hip surgery within the next 2 years. Ethics approval was received from The Tasmania Health and Human Ethics Committee (reference number H1040). Written informed consent was obtained from all participants.

6.3.3 Randomisation and blinding

Participants were randomly assigned to a vitamin D or a placebo group using computer-generated allocation with a 1:1 ratio. Allocation concealment was ensured by using a central automated process independent of the investigators. Participants, investigators and research coordinators were all blinded to the treatment allocation. Blinding for both the main study and for the trunk muscle outcomes was maintained until all data were collected, cleaned, confirmed for accuracy and statistical analysis were completed.

6.3.4 Interventions

Participants in the treatment group were given one 50,000 IU (1.25 mg) vitamin D3 (cholecalciferol) capsule per month, for 24 months. Participants in the control group were given an identical inert placebo. The vitamin D3 compound and inert placebo were acquired from Nationwide Compounding Pharmacy, Melbourne, Australia. [221]

6.3.5 Outcomes

Primary outcome measures in this pre-specified secondary analysis were between-group differences in change in muscle morphology: a- changes in muscle thickness of the abdominal muscles (rectus abdominis (RA), transversus abdominis (TrA), internal oblique (IO), external oblique (EO)) and the lumbar multifidus (MF) muscles; b- changes in cross-sectional area (CSA) of the MF muscles and c- changes in muscle thickness with contraction of the abdominal muscles (except RA) and the MF muscles from baseline to 12 months.

6.3.6 Image capture and measurement

Ultrasound muscle images were taken using a Phillips HDI 5000 ultrasound machine (Bothwell, WA, USA) in brightness mode (B-mode) with a handheld 4-7 MHz broadband curved array transducer. Image capture and measurement of the abdominal wall and MF muscles was undertaken following previously published protocols [121, 122, 185, 264, 266, 298, 301, 315-317]. The ultrasound imaging (USI) assessments were conducted by a physical therapist who undertook 36 hours of practical training in USI at the beginning of the project.

Muscles of the abdominal wall were imaged in transverse section. Participants were positioned in supine lying, with a pillow under their knees [121, 298]. To elicit a voluntary contraction of the abdominal wall, participants were asked to "take a relaxed breath in and out, hold your breath out, and then draw in your lower abdomen without moving your spine" [298]. The RA muscles were only imaged at rest, and the TrA, IO and EO muscles were imaged at rest and on contraction. [121]

Imaging of the lumbar multifidus muscles was performed with participants positioned in prone lying, with a pillow placed under their abdomen to reduce lumbar lordosis [122, 301, 317]. Images of the lumbar MF muscles were captured both at rest (in the transverse plane) and during contraction (in the parasagittal plane). Instructions for the isometric contraction were "take a relaxed breath in and out, hold your breath out and try to slowly "swell" and contract the muscle without moving the spine" [174].

Ultrasound images were stored and later analysed offline by a single examiner using a software package (Image J Image Processing and Analysis, version IJ 1.46r, http://imagej.nih.gov/ij/). The thickness of the abdominal muscles was measured as the perpendicular distance between the superior and inferior hyperechoic muscle fascias at approximately the middle of the image identified using the software's Cartesian coordinates [298]. The CSA of the MF muscle was

measured by tracing around the inner edge of the fascial boundaries of the muscle [122, 315] and the thickness of the MF muscle was measured from the tip of the zygapophyseal joint to the inferior fascial edge of the superior border of the muscle [301]. Intraclass correlation coefficients (ICC) for abdominal and MF muscle measurements were ICC= > 0.85 for interrater USI image measurement reliability [266], and ICC= 0.74-0.98 for test-retest reliability [264].

6.3.7 Other factors

Height was measured by stadiometer to the nearest 0.1 cm (Leicester Height Measure, Invicta Plastics Ltd, Leicester, UK). Weight was measured by calibrated scales (Heine S-7307, Heine, New Hampshire, USA) and BMI was calculated (weight (kg)/height (m^2)). Knee pain scores were obtained using a visual analogue pain scale in 100 mm, assessing pain during walking, using stairs, in bed, sitting or lying and standing. The total pain score was calculated as the sum of the 5 items (range 0-500) [294]. Total WOMAC score was calculated as the sum of the scores in each of its subscales that included pain, stiffness and physical function. Missing data were managed according to the WOMAC user guide [294]. Physical activity was measured using the short version of the International Physical Activity Questionnaire (IPAQ) instrument. Data were collected on vigorous and moderate activity as well as walking and sitting, but data on sitting were not used in the analysis. Total IPAQ scores were calculated according to published guidelines [293, 318]. Current low back pain status was assessed by a questionnaire asking, “do you currently have any pain in your back?”, and pain scores were obtained using a Visual Analogue Scale (0-100 mm). History of back surgery, abdominal surgery and medications were obtained by questionnaire. Leg strength measures to the nearest kilogram were obtained for both legs simultaneously using a dynamometer (TTM Muscular Meter, Tokyo, Japan) as described by Scott et al. [296]. This is an isometric strength muscle test, predominantly for the quadriceps and hip extensor muscles. Grip strength was assessed with a hand-held dynamometer.

6.3.8 25-Hydroxyvitamin D

Serum25-hydroxyvitamin D was assayed at screening, 3 months, and 24 months. Blood samples were centrifuged after standing for 10 minutes at room temperature and the resultant serum frozen at -80C until assayed using direct competitive chemiluminescent immunoassays (DiaSorin Inc). The intraassay and interassay coefficients of variation were 3.2% and 6.0% [292].

6.3.8 Sample size

Calculations were based on the standard deviations reported by Rankin et al [121] for the thickness of the abdominal muscles and by Wallwork et al [299] for thickness and CSA of the lumbar multifidus. Correlations between measurements and re-measurement of r = 0.9 for abdominal muscle thickness, r = 0.5 for multifidus thickness and r = 0.7 for multifidus CSA, were observed in our reliability study [264]. On that basis, this study of projected size 200 subjects (100 in each arm) would have 80% power to detect between-group differences of 0.02 to 0.05 cm for change in abdominal muscle thickness, 0.20 to 0.21 cm for change in multifidus thickness, and 0.28 to 0.40 cm^2 for change in multifidus CSA.

6.3.9 Statistical analysis

As summary measures of their distributions, means and standard deviations were used for continuous measures, and percentages and frequencies were used for categorical factors. Random intercept linear mixed models were used to estimate the change between baseline and follow-up in both treatment arms, and the difference in change for the treatment groups, in this intention-to-treat analysis. The models included binary terms for side (left or right) in measurements of muscle thickness and CSA, and for state (relaxed or contracted) of muscle thickness. Changes in muscle morphology, that is thickness and CSA in the relaxed state, and change in function (assessed by changes in muscle thickness on contraction) were compared for each group of participants. Because there was no statistically significant differences between the 2 sides for either group, the means of the right and left muscle sizes were used in the analysis. In additional analyses, adjustments were made for age, sex and BMI (pre-specified in the protocol) and for additional factors that were potential confounders and for which there was an imbalance between the treatment arms. Only the adjustment for lower limb strength resulted in a marked change in the estimated effect of the intervention (see Table 1). To test for interaction by serum 25(OH)D status at baseline, a binary term generated using a serum 25(OH)D cut-point of 25 nmol/L (10 ng/mL) was included as a covariate and as a component of a product term in the regression model. Similarly, testing for interaction by BMI category (normal (≤25 kg/m^2), overweight (>25 - <30 kg/m^2) and obese (≥30 kg/m^2)) was performed. The step-down procedure of Holm [319] was used to control the family-wise error rate (table 3). Statistical analyses were performed using Stata (Version 14.0, Stata Corporation, TX, USA) and a two-sided p-value of 0.05 was deemed statistical significance.

6.4 Results

Of the 422 potential VIDEO participants screened at the Hobart site, 265 were randomised and assigned to the treatment or placebo groups. Of these, 104 participants in the treatment group (39.3%) and 113 participants in the placebo group (42.6%) had images of their trunk muscles taken at baseline for this sub-study. Ninety-five and ninety-one participants had trunk muscle images taken at follow-up one year later in the treatment and placebo groups respectively (Figure 1).

Table 1 summarises the baseline characteristics of participants in the treatment and placebo groups in this sub-study. The groups were reasonably well matched, with some difference in proportions for gender, low back pain, history of abdominal surgery, statins use and lower limb strength. Overall knee pain scores measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were in the low ranges (122/500), while physical activity levels measured by the international physical activity questionnaire (IPAQ) were in the higher ranges (>3000 MET-minutes/week) [293]. Mean serum 25(OH)D levels in the vitamin D group increased by 39.3 nmol/L (15.6 ng/ml) and 44.5 nmol/L (18.0 ng/ml) at 3 and 24 months respectively, compared with an initial increase of 17.6 nmol/L (7.2 ng/ml) at 3 months and a total increase of 6.8 nmol/L (2.8 ng/ml) at 24 months in the placebo group. There were no baseline differences between the participants in this sub-study and the entire VIDEO cohort (n=413) [292]. The BMI of the study population was relatively high (over 85% were overweight or obese). In the 172 participants of this US sub-study who had serum 25(OH)D measured at 24 months, increase in serum 25(OH)D levels from baseline to 24 months in overweight (>25 - <30 kg/m2) and obese (⩾30 kg/m2) was 8.7 nmol/L (3.6 ng/ml) and 5.2 nmol/L (2.0ng/ml) lower respectively than in participants with normal BMI (⩽25 kg/m2) and those. In fact, 76% of the treatment group achieved serum 25(OH)D levels ⩾ 75 nmol/L (⩾30 ng/ml) by 24 months compared with only 7% of the placebo group, the former including 25/33 (76%) of obese, 22/33 (67%) of overweight treatment arm participants.

The between-group treatment effects for trunk muscle size and change in thickness with contraction were small (less than 4% in each muscle), inconsistent in direction and not statistically significant (Table 2 and 4). Adjusting for age, sex and BMI did not change these results (Table 3 and 5). While additional adjustment for leg strength increased the effect size for multifidus thickness at the L2/L3, L3/L4 and L4/L5 vertebral levels, the only between-group difference that was statistically significant after controlling for family-wise error was at the

L2/L3 vertebral level and the effect size (3.5%) remained small (Table 3 and 5). Results were similar after further adjustments for statin use, current low back pain, and history of abdominal or back surgery. There were not significant within-group differences in trunk muscle size or function over 12 months in either group. There were no interactions between treatment effect and either baseline 25(OH)D status or BMI in adjusted analyses for any muscle measure (all $p<0.05$).

6.4.1 Adverse events

A description of adverse events for the full clinical trial has been reported previously [292]. In this sub-study, 44 (42%) out of 104 participants in the vitamin D group reported adverse events compared with 30 (27%) out of 113 participants in the placebo group (Table 6). Two cases of hypercalcemia were reported in each group. One instance of hyperthyroidism and two episodes of renal calculus were reported in the vitamin D group [292]

6.5 Discussion

To our knowledge, this is the first RCT investigating the effect of vitamin D supplementation on the morphology of key postural trunk muscles of older adults. Apart from the thickness of the MF muscles at the L2-L3 vertebral level, there were no statistically significant differences in change in muscle thickness or CSA between the vitamin D and placebo groups, and all effect sizes were small and not clinically significant. The results suggest that vitamin D supplementation alone is not an effective means to improve or maintain trunk muscle size over time for adults aged 50-79 years, even for those individuals with moderate to severe deficiency.

The purpose of this study was to determine whether vitamin D supplementation alone had beneficial effects in maintaining or improving trunk muscle size and function. In the present study, the within-group changes in trunk muscle size and function over time were all very small. Despite there being plausible reasons to hypothesise that vitamin D supplementation could improve trunk muscle size, our results suggest that increases or maintenance of muscle size or function of older adults cannot be expected from vitamin D supplementation alone, at least over the limited timeframe of one year. In peripheral muscles, two systematic reviews reported positive effects of vitamin D supplementation on muscle strength in older adults with baseline 25(OH)D <30 nmol/L (<12 ng/ml) [206, 216]. However, in our study of trunk muscles, the response to supplementation did not vary between people with moderate to severe deficiency (25(OH)D (<25 nmol/L, <10 ng/ml) at baseline and those with 25(OH)D levels above this level. Thus, even in people with this degree of deficiency, vitamin D supplementation does not

improve trunk muscle size or muscle function as assessed by change in muscle thickness during submaximal contraction.

Whilst there is no consensus on the amount of variation in trunk muscle size required to ascertain clinically meaningful changes in these muscles [121], previous studies investigating the effect of exercise programs on trunk muscles in people with low back pain have found interventions that increased muscle size were associated with decreases in pain [174, 320, 321]. The changes in muscle sizes observed in those studies were larger than those seen in our study, for example being over 5% for measures of the multifidus and transversus abdominis muscles at rest [174, 320]. Thus, exercise programs or a combination of exercise and functional activities that target trunk muscles may be more effective in improving these muscles than vitamin D supplementation alone.

The effects of vitamin D supplementation on peripheral muscle strength, mass and power have been examined in a systematic review and meta-analysis [216]. The studies in this review administered a wide range of vitamin D doses (as low 300 IU per day, up to intermittent doses equivalent to around 8600 IU/day). For muscle strength, there was a small but statistically significant positive effect of vitamin D supplementation on lower limb muscle strength (19 studies in 2349 people; vitamin D dose range 400 to 8600 IU; standard mean difference (SMD)= 0.19 (95% CI 0.05–0.34)). However, there was no statistically significant effect of vitamin D supplementation on grip strength (16 studies, doses 400-8600 IU/d) nor on muscle mass (6 studies, n=538, doses 300-4000 IU/d) or power (5 studies, n=245, doses 400-4000 IU/d). The latter is consistent with the lack of effect on muscle size observed in the current study, but as trunk muscle strength and power were not measured in our study, it remains to be determined whether vitamin D supplements affect strength or power in trunk muscles.

Previous studies have reported improvements in measures of functional mobility (walking test and “timed up and go” test) and reduced risk of falls with vitamin D supplementation of older adults [56, 314]. Although the present study did not investigate the effect of vitamin D supplementation on falls or functional mobility, our results suggest changes to these outcomes are not mediated by trunk muscle size. The effect of vitamin D supplementation on other aspects of trunk muscle function such as strength cannot be ruled out and should be the focus of future research.

6.6 Strengths and Limitations

The strength of the current investigation is its design. It is a double-blind randomised controlled trial, which provides robust evidence regarding the efficacy of vitamin D supplementation for improving trunk muscle size. Participants in this study were community-dwelling adults with low serum 25(OH)D. This is the sub-population most likely to benefit from vitamin D supplementation.

It has limitations nevertheless. While the use of random allocation helps to reduce the possibility of imbalance between the treatment arms, in this case, randomisation did not produce exact balance. However, we collected information that made it possible to adjust for these factors and the results of the adjusted analyses did not alter the overall conclusions of the study. While the study sample was on average only mildly deficient, there was no interaction between treatment response and vitamin D status at baseline, suggesting that the results are generalizable to both mildly and moderately deficient people. While our sample size was modest, we powered the study appropriately to detect treatment effects that were likely to be clinically meaningful based on existing literature [174, 320, 322]. We are therefore unlikely to have failed to detect any clinically important treatment effects. The majority of participants were either overweight or obese, which could have influenced their serum 25(OH)D response to supplementation. However, participants with high BMI still achieved large increases in 25(OH)D and a much higher proportion of these participants reached levels ≥ 75 nmol/L (≥30 ng/ml) than in the placebo group. Furthermore, there was no interaction between treatment response and BMI, so the impact of being an obese population on our results was minimal. The lack of any interaction also suggests that our results are generalizable to people with OA who are of normal weight. It is possible mobility restrictions from knee OA may have affected participants' ability to improve trunk muscle size. Nevertheless, levels of knee pain in the study were relatively low, functional limitations were modest and physical activity levels reasonable, which makes this scenario unlikely. We used a DiaSorin immunoassay method to measure serum 25(OH)D, rather than mass spectrometry which is considered the gold standard. However, mass spectrometry is not readily available in clinical practice, which would affect translation into practice and a recent study found that the DiaSorin immunoassay achieved acceptable performance when compared to mass spectrometry [323]. Our only measure of muscle function was change in muscle thickness with contraction so we cannot rule out effects of vitamin D supplementation on other aspects of muscle function such as strength, power, physical function or falls.

6.7 Conclusion

There is no evidence that a monthly dose of 50,000 IU of vitamin D3 alone has an effect on the size or ability to contract trunk muscles of independent, community-dwelling older adults with symptomatic knee osteoarthritis and low serum 25(OH)D levels regardless of BMI status or degree of vitamin D deficiency. An effect of vitamin D supplementation on other aspects of trunk muscle function such as strength, power or physical function cannot be ruled out.

6.8 Other information

6.8.1 Author contributions

Study conception and design:	TMW, GJ, JAH, CD, FC, AW
Project management of study during implementation:	TMW, CD, GJ
Acquisition of data:	WAC
Design of data analysis plan:	WAC, LB, JAH, MLC, TMW
Analysis and interpretation of data:	WAC, LB, JAH, MLC, TMW
Drafting and revisions of manuscript:	WAC, LB, JAH, MLC, GJ, TMW, CD, FC, AW

All authors approved the final version of the manuscript.

6.8.2 Conflicts of Interest and Sources of Funding:

All authors declare no conflict of interest. This study was supported by a grant from the Australian National Health and Medical Research Council (NH&MRC). The funder of this study had no involvement in study design, collection of data, interpretation of data or writing of the report. TMW is supported by a National Health and Medical Research Council (NHMRC)/Primary Health Care Research Evaluation and Development Program Career Development Fellowship. CLB is supported by a Career Development Fellowship from NH&MRC. GJ is supported by an NHMRC Practitioner Fellowship. AEW is supported by a National Health and Medical Research Council (NHMRC) Career Development Fellowship (Clinical Level 2).

6.8.3 Trial registration

ClinicalTrials.gov identifier: NCT01176344;

Australian New Zealand Clinical Trials Registry: ACTRN12610000495022.

6.8.4 Protocol

Cao Y, Jones G, Cicuttini F, et al. Vitamin D supplementation in the management of knee osteoarthritis: study protocol for a randomized controlled trial. Trials 2012;13:131.

6.8.5 Authorship statement

The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle [324]

Table 6.1 Baseline characteristics of vitamin D and placebo groups

	Vitamin D (n=104)	Placebo (N=113)
Male sex % (n/N)	53 (55/104)	51 (58/113)
Age (yrs.)	63.7 (7.4)	63.0 (7.3)
Weight (kg)	84.4 (15.5)	84.4 (15.1)
Height (cm)	169.1 (10.2)	170.0 (9.7)
BMI (kg/m^2)	29.5 (5.3)	29.5 (4.5)
BMI ≤25 kg/m^2 % (n/N)	15 (16/104)	11 (12/113)
BMI >25 - <30 kg/m^2 % (n/N)	47 (49/104)	43 (49/113)
BMI ≥30 kg/m^2 % (n/N)	38 (39/104)	46 (52/113)
25-hydroxyvitamin D (nmol/L)	42.5 (12.0)	43.9 (12.1)
Total knee WOMAC score (0-2400)	576.3 (394.9)	571.7 (373.3)
Pain (0-500)	121.3 (88.3)	122.7 (84.5)
Stiffness (0-200)	52.6 (41.9)	58.1 (40.5)
Function (0-1700)	402.4 (287.0)	390.9 (274.7)
Physical activity – IPAQ score	3628.9 (4762.0)	3057.6 (3054.0)
Current low back pain %(n/N)	39 (41/104)	34 (38/113)
Current low back pain - VAS score	28.0 (19.3)	28.3 (22.0)
History of low back surgery: % (n/N)	6 (6/104)	11.0 (12/113)
History of abdominal surgery: % (n/N)	55 (57/104)	50 (56/113)
Medication: Statins % (n/N)	6.7 (7/104)	12.0 (13/113)
Lower limb strength (kg)	67.1 (42.9)	70.0 (44.8)
Grip strength: right (kg)	30.7 (12.3)	30.8 (11.0)
Grip strength: left (kg)	29.7 (12.0)	29.7 (11.1)

All results reported mean (standard deviation) or % (n/N) where indicated. *BMI:* body mass index. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. IPAQ: International physical activity questionnaire (MET-minutes/week) *VAS*: visual analogue scale (0-100 where 0=no pain and 10=very worst pain).

Figure 6.1 Flowchart of participants

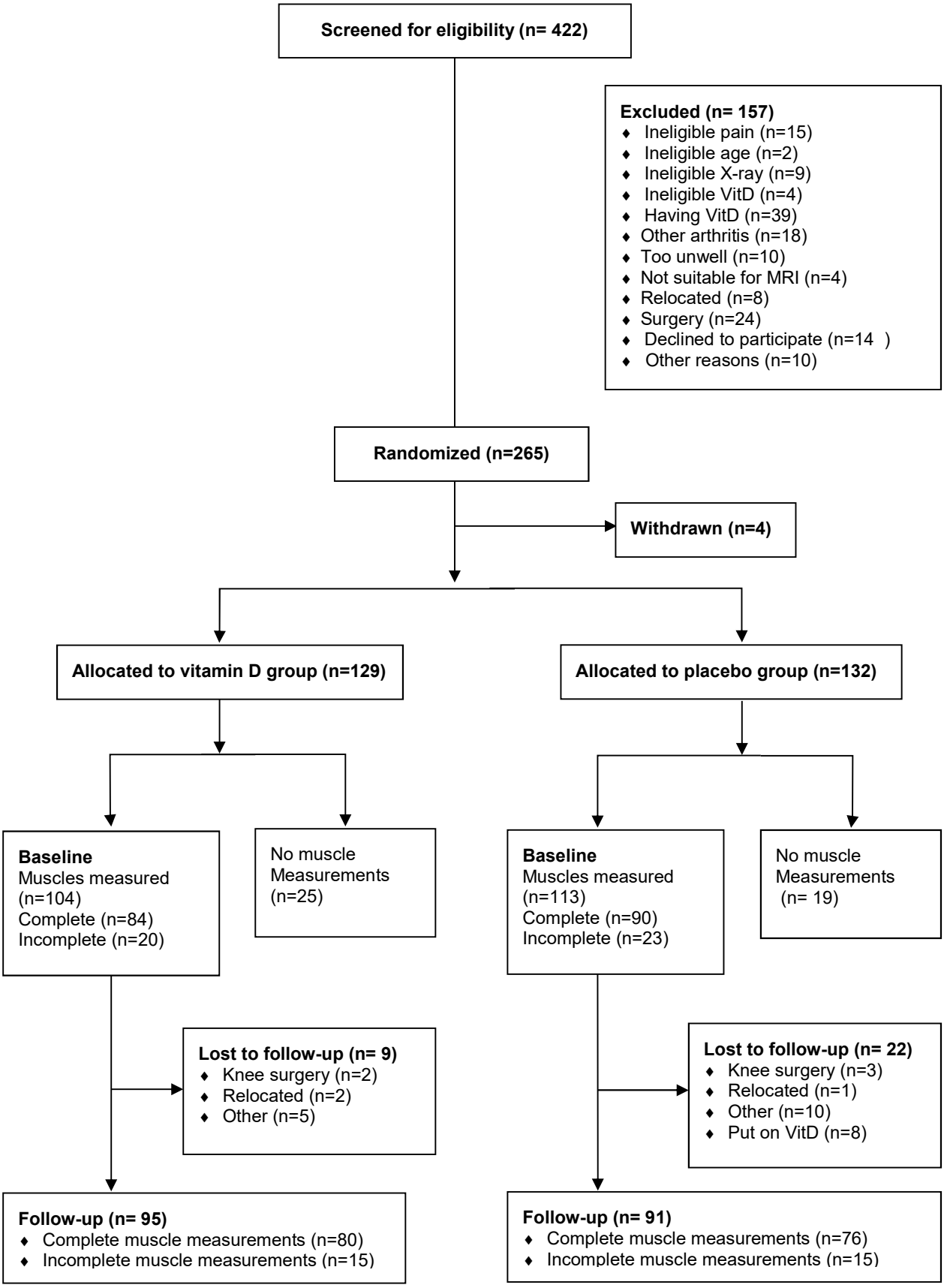


Table 6.2 Changes in relaxed abdominal muscle thickness (cm) and in change in muscle thickness with contraction from baseline to follow-up by intervention group

	Vitamin D group			Placebo Group			Between-group differences in change
Muscle	Baseline	Follow up	Change	Baseline	Follow up	Change	
RA	0.827 (0.019)	0.845 (0.019)	0.017 (0.008)	0.850 (0.018)	0.860 (0.018)	0.010 (0.008)	0.007 (0.011)
TRA (relaxed)	0.380 (0.011)	0.390 (0.012)	0.011 (0.007)	0.409 (0.011)	0.427 (0.011)	0.018 (0.007)	-0.007 (0.010)
TRA *	0.168 (0.009)	0.187 (0.009)	0.018 (0.008) †	0.153 (0.008)	0.176 (0.009)	0.023 (0.009) †	-0.005 (0.012)
IO (relaxed)	0.775 (0.024)	0.752 (0.025)	-0.023 (0.015)	0.851 (0.023)	0.845 (0.024)	-0.006 (0.015)	-0.017 (0.021)
IO *	0.221 (0.019)	0.243 (0.019)	0.015 (0.016)	0.203 (0.018)	0.243 (0.019)	0.039 (0.016) †	-0.024 (0.022)
EO (relaxed)	0.431 (0.013)	0.432 (0.013)	0.001 (0.008)	0.451 (0.012)	0.462 (0.013)	0.011 (0.008)	-0.010 (0.011)
EO *	0.075 (0.009)	0.091 (0.010)	0.016 (0.010)	0.085 (0.009)	0.093 (0.010)	0.009 (0.010)	0.007 (0.014)

All measures are in cm, and are reported as mean (standard error)
Abbreviations: *RA,* rectus abdominis; *TrA,* transversus abdominis; *IO,* internal oblique; *EO,* external oblique
* Absolute change in muscle thickness with contraction, calculated as (thickness when contracted – thickness when relaxed)
† Statistically significant $p<0.05$

Table 6.3. Between group differences in changes in relaxed abdominal muscle thickness (cm) and in change in muscle thickness with contraction from baseline to follow-up without and with adjustment for relevant factors

		Adjusted for	
Muscle	Unadjusted model	Age + Sex + BMI	Age + Sex + BMI + Leg strength
RA	0.007 (-0.015, 0.029)	0.010 (-0.012, 0.032)	0.009 (-0.015, 0.032)
TRA (relaxed)	-0.007 (-0.027, 0.013)	-0.004 (-0.024, 0.016)	-0.007 (-0.029, 0.014)
TRA *	-0.005 (-0.028, 0.019)	-0.004 (-0.028, 0.019)	-0.004 (-0.030, 0.021)
IO (relaxed)	-0.017 (-0.058, 0.024)	-0.013 (-0.054, 0.028)	-0.010 (-0.054, 0.034)
IO *	-0.024 (-0.068, 0.020)	-0.022 (-0.066, 0.022)	-0.021 (-0.069, 0.026)
EO (relaxed)	-0.010 (-0.032, 0.126)	-0.008 (-0.030, 0.015)	-0.010 (-0.034, 0.013)
EO *	0.007 (-0.019, 0.034)	0.006 (-0.021, 0.034)	0.011 (-0.017, 0.040)

All measures are in cm and are reported as mean (confident interval)
Abbreviations: *RA,* rectus abdominis; *TrA,* transversus abdominis; *IO,* internal oblique; *EO,* external oblique
* Absolute change in muscle thickness with contraction calculated as (thickness when contracted – thickness when relaxed)
† Statistically significant $p<0.05$

Table 6.4 Changes in relaxed multifidus muscle thickness (cm), changes in muscle thickness with contraction and in changes cross-sectional area (cm2) from baseline to follow-up by intervention group

	Vitamin D group			Placebo Group			Between-group differences in change
Muscle	Baseline	Follow up	Change	Baseline	Follow up	Change	
Muscle thickness							
L2/L3_MF (relaxed)	2.646 (0.046)	2.649 (0.047)	0.003 (0.043)	2.670 (0.044)	2.580 (0.047)	-0.090 (0.043)	0.092 (0.060)
L2/L3_MF *	0.140 (0.018)	0.115 (0.018)	-0.025 (0.019)	0.167 (0.017)	0.142 (0.018)	-0.025 (0.019)	-0.000 (0.026)
L3/L4_MF (relaxed)	2.331 (0.043)	2.428 (0.044)	0.097 (0.036) †	2.339 (0.041)	2.409 (0.043)	0.070 (0.036)	0.027 (0.051)
L3/L4_*	0.134 (0.018)	0.129 (0.018)	-0.005 (0.021)	0.145 (0.017)	0.124 (0.018)	-0.020 (0.021)	0.015 (0.029)
L4/L5_MF (relaxed)	2.864 (0.048)	2.817 (0.049)	-0.047 (0.045)	2.913 (0.046)	2.842 (0.049)	-0.071 (0.046)	0.024 (0.064)
L4/L5_MF *	0.168 (0.018)	0.160 (0.019)	-0.008 (0.019)	0.184 (0.018)	0.180 (0.019)	-0.005 (0.019)	-0.003 (0.027)
L5/S1_MF (relaxed)	2.744 (0.049)	2.863 (0.051)	0.119 (0.044) †	2.758 (0.047)	2.925 (0.050)	0.167 (0.045) †	-0.048 (0.063)
L5/S1_MF *	0.138 (0.019)	0.153 (0.020)	0.015 (0.021)	0.170 (0.018)	0.178 (0.020)	0.008 (0.021)	0.007 (0.030)
Cross-sectional area							
L2_MF_CSA	2.670 (0.054)	2.858 (0.055)	0.188 (0.027)	2.654 (0.052)	2.908 (0.053)	0.254 (0.027)	-0.066 (0.038)
L3_MF_CSA	3.500 (0.061)	3.830 (0.062)	0.330 (0.037)	3.423 (0.058)	3.774 (0.060)	0.350 (0.038)	-0.021 (0.053)
L4_MF_CSA	4.416 (0.068)	4.831 (0.069)	0.415 (0.038)	4.230 (0.065)	4.708 (0.067)	0.478 (0.039)	-0.063 (0.054)
L5_MF_CSA	5.211 (0.081)	5.519 (0.082)	0.307 (0.048)	4.979 (0.077)	5.399 (0.080)	0.420 (0.049)	-0.112 (0.068)

All measures are in cm, and are reported as mean (standard error)
Abbreviations: MF, multifidus muscle; CSA, cross-sectional area
* Absolute change in muscle thickness with contraction calculated as (thickness when contracted – thickness when relaxed)
† Statistically significant $p<0.05$

Table 6.5 Between group differences in change in relaxed multifidus muscle thickness (cm), in change in muscle thickness with contraction and cross-sectional area (cm2) from baseline to follow-up without and with adjustment for relevant factors

		Adjusted for	
Muscle	Unadjusted model	Age + Sex + BMI	Age + Sex + BMI + Leg strength
Muscle thickness			
L2/L3_MF (relaxed)	0.092 (-0.026, 0.211)	0.115 (-0.004, 0.234)	0.172 (0.048, 0.296) † ‡
L2/L3_MF *	-0.000 (-0.052, 0.051)	-0.115 (-0.054, 0.051)	-0.176 (-0.073, 0.037)
L3/L4_MF (relaxed)	0.027 (-0.073, 0.127)	0.038 (-0.063, 0.139)	0.054 (-0.052, 0.161)
L3/L4_MF *	0.015 (-0.042, 0.072)	0.017 (-0.041, 0.074)	-0.001 (-0.062, 0.060)
L4/L5_MF (relaxed)	0.024 (-0.102, 0.150)	0.050 (-0.076, 0.176)	0.089 (-0.045, 0.222)
L4/L5_MF *	-0.003 (-0.056, 0.050)	0.003 (-0.049, 0.056)	0.025 (-0.054, 0.059)
L5/S1_MF (relaxed)	-0.048 (-0.172, 0.076)	-0.028 (-0.152, 0.096)	-0.015 (-0.146, 0.117)
L5/S1_MF *	0.007 (-0.052, 0.066)	0.015 (-0.043, 0.073)	0.017 (-0.044, 0.078)
Cross-sectional area			
L2_MF_CSA	-0.066 (-0.142, 0.009)	-0.059 (-0.135, 0.017)	-0.060 (-0.140, 0.020)
L3_MF_CSA	-0.021 (-0.125, 0.083)	-0.016 (-0.120, 0.089)	0.039 (-0.069, 0.147)
L4_MF_CSA	-0.063 (-0.169, 0.043)	-0.062 (-0.168, 0.045)	-0.041 (-0.148, 0.067)
L5_MF_CSA	-0.112 (-0.246, 0.022)	-0.129 (-0.260, 0.003)	-0.120 (-0.259, 0.019)

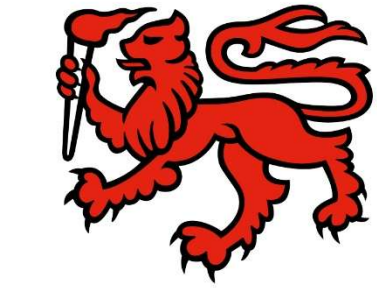
All measures are in cm and are reported as mean (standard error)
Abbreviations: MF, multifidus muscle; CSA, cross-sectional area
* Absolute change in muscle thickness with contraction calculated as (thickness when contracted – thickness when relaxed)
† Statistically significant $p<0.05$

Table 6.6 Adverse events

	Vitamin D	(N=104)	Placebo	(N=113)
	No. of participants	(%)	No. of participants	(%)
Serious Adverse Events				
Death	1	(1.0)	0	(0.0)
Malignancy	2	(1.9)	2	(1.8)
Coronary artery disease	1	(1.0)	1	(0.9)
Severe infection	0	(0.0)	1	(0.9)
Major depression	1	(1.0)	0	(0.0)
Nephrolithiasis	1	(1.0)	1	(0.9)
Hospitalization	1	(1.0)	0	(0.0)
Adverse Events				
Hypercalcemia	2	(1.9)	2	(1.8)
Hyperparathyroidism	1	(1.0)	0	(0.0)
Renal	2	(1.9)	0	(0.0)
Falls	2	(1.9)	0	(0.0)
Musculoskeletal	1	(1.0)	1	(0.9)
Neurological	1	(1.0)	1	(0.9)
Gastrointestinal	1	(1.0)	3	(2.7)
Respiratory	2	(1.9)	1	(0.9)
Ocular	1	(1.0)	1	(0.9)
Infection	4	(3.9)	2	(1.8)
Cardiac arrhythmia	1	(1.0)	0	(0.0)
Chest pain	4	(3.9)	4	(3.5)
Pain	6	(5.8)	2	(1.8)
Allergy/immunology	0	(0.0)	2	(1.8)
Other events^	9	(8.7)	6	(5.3)

^Including headache, lethargy, flu symptoms and other events.

CHAPTER 7 - ASSOCIATIONS BETWEEN ABDOMINAL AND MULTIFIDUS MUSCLE SIZE AND PHYSICAL ACTIVITY, PHYSICAL FUNCTION AND QUALITY OF LIFE AMONG ADULTS AGED 50-79 YEARS: A CROSS-SECTIONAL STUDY



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7.1 Prelude

Having studied the effects of Vitamin D supplementation on trunk muscle size, we proceeded to investigate another important gap in the literature identified in both the second section of the introduction chapter and the systematic review. As discussed in the second section of the introductory chapter, there was limited evidence for associations between trunk muscle measures and measures of physical function in older adults. The evidence is also conflicting, with studies reporting positive [7, 137, 271, 313] and negative [145, 325] associations between measures of muscle size and composition and measures of physical function. The limited number of studies investigating the role that trunk muscle morphology plays in the physical function of older adults prompted us to address this important gap in the literature. Therefore, the study in this chapter aimed to evaluate cross-sectional associations between trunk muscle size and muscle function with measures of physical activity, physical function and quality of life in a sample of community-dwelling adults aged 50 – 79, with knee osteoarthritis and low-level serum 25(OH)D. The following text in this chapter is in the last stages of preparation prior to submission to a peer review journal.

7.2 Introduction

Ageing has a detrimental effect on the mass, strength and size of upper and lower limb muscles, which is associated with deterioration in physical activity, physical function and quality of life, as well as an increase in fear of falling among older adults [11-15]. Like peripheral muscles, there are age-related decreases in trunk muscle size and muscle function, reflected in the ability of people to activate their muscles to adjust posture and centre of gravity following external disturbances [138, 140-142]. Muscles of the trunk are important for an individual's ability to perform fundamental functional activities of daily living due to the complex role they play in load transfer, force dissipation, stability of the spine, control of balance and posture, and trunk and pelvic movement [6, 8, 9]. In older adults, there is evidence for a detrimental effect on the size, composition and activation of the MF muscle by conditions which limit physical function, such as lumbar spine degeneration, degenerative lumbar scoliosis and low back pain [138].

The trunk muscles investigated in this study included the rectus abdominis (RA), transversus abdominis (TrA), internal oblique (IO), external oblique (EO) and the lumbar multifidus (MF) muscles. The superficial abdominal muscles are torque producers of the trunk, while the deep abdominal and MF muscles are tonically active during weight bearing activities [76, 77, 132, 133, 135].

The MF muscle was chosen because of its prominent role in the function of the lumbar spine [149]. It transfers loads through the lower spine and has a dual role as stabiliser of the spine, controlling intersegmental motion via its deep muscle fibres and generating trunk extension and control of posture and spine orientation via its superficial fibres [105, 107-109].

There are few studies addressing whether size, activation and muscle quality of these trunk muscles are associated with measures of physical function in older adults. Some studies have reported negative associations between intramuscular fat infiltrations (muscle attenuation (MA)) in abdominal and MF muscles and measures of physical function (Short Physical Performance Battery (SPPB), gait speed, timed up and go test (TUG) and stair descent test) [145, 146, 325] and balance [271] in people with chronic low back pain (CLBP). However, it is not known whether these associations are similar in healthy, active, community dwelling older adults. These studies also demonstrate a lack of association between MF muscle size and measures of physical function in people with CLBP [145, 146, 271, 325]. Contrary to these findings, a recent study reported significant positive associations between the RA muscle size and measures of functional mobility in community-dwelling adults aged 65 years and over [313], indicating a possible mediating role of trunk muscle size on the physical function of older adults. Understanding the role abdominal and MF muscle size and function play in healthy ageing and physical function of older adults is important, as these muscles are a potential target for interventions to improve or prevent the detrimental effect that age has on functional living. Therefore, the aim of this study was to investigate associations between abdominal and MF muscle size and the ability to contract these muscles (muscle function) and measures of physical activity, physical function and quality of life among active older adults.

7.3 Methods

7.3.1 Participants

Participants were part of an ultrasound imaging (USI) sub-study of trunk muscles (n=217) conducted on participants from the "Vitamin D Effect on Knee Osteoarthritis" (VIDEO) clinical trial at the Tasmanian site [292]. The VIDEO study was a randomised, placebo-controlled and double-blind clinical trial conducted between 2010 and 2013. The detailed study protocol, including inclusion and exclusion criteria, has previously been published [221]. In brief, VIDEO participants were 50-79 year-old adults recruited from the general community in Tasmania and Victoria who had ongoing symptoms of knee osteoarthritis (OA) for at least six months, serum 25-(OH)D levels between 12.5 and 60 nmol/L (5 to 24 ng/ml) and pain levels between 20-80 mm

on a 100 mm visual analogue scale (VAS) at baseline. Exclusion criteria included severe radiographic knee OA, severe pain (> 80 mm on a 100 mm VAS) on standing, hypersensitivity to vitamin D, any condition affecting oral drug absorption and anticipated need for knee or hip surgery within the 2-year duration of the clinical trial. Participants were randomly assigned to either a vitamin D treatment group (one 50,000 IU vitamin D3 capsule per month, for 24 months) or a placebo group (identical inert placebo) using computer-generated allocation with a 1:1 ratio [221]. The Tasmania Health and Human Ethics Committee approved this study. All participants gave written informed consent.

7.3.2 Physical activity, physical function and quality of life

Physical activity was assessed by the International Physical Activity Questionnaire (IPAQ) and by pedometers. Participants self-reported information on vigorous and moderate activity as well as walking and sitting using the short form of IPAQ, which has been found to be valid and reliable [318, 326]. Information on sitting was not included in the summary score of physical activity as per IPAQ guidelines [293, 318]. Total summary scores for physical activity (MET/hour/week) were calculated following published guidelines [293, 318].

Digi-Walker SW-200 (Yamax) pedometers were used to measure ambulatory physical activity. Participants recorded start and end times of usage each day, and total daily steps for 7 days. Daily entries were excluded for 4.3% (75/1742) of recordings as the pedometer was worn less than 8 hours, which was determined not to represent a full day [327]. A cap was not applied because the maximum recorded steps per day entry were <20000. Average daily steps were calculated for participants who recorded at least 5 daily readings [328]. Pedometer data from 26 participants were omitted from the analysis as they did not meet the 5-day reading criterion.

Deficits in physical function were assessed by the functional deficit subscale of the Western Ontario and McMaster Universities Arthritis Index (WOMAC). The WOMAC is an osteoarthritis (OA) specific instrument widely used to assess the progression of disease symptoms and evaluate interventions. Its reliability and validity have been extensively tested [329-331]. The WOMAC version used in this study had three subscales; pain (5 questions), stiffness (2 questions) and functional deficit (17 questions). The functional deficit subscale scores were used in this analysis. In this subscale, participants are asked how knee pain interfered with their physical function, specifically asking “Referring to your knees only, how much functional deficit do you experience when: descending stairs, ascending stairs, rising from bed, rising from sitting, putting on socks, taking off socks, bending to the floor, lying in bed, walking on flat surface,

getting in/out of the bath, standing, sitting, getting in/out of the car, getting on/off the toilet, heavy domestic chores, light domestic chores and shopping". Each of the 17 functional deficit items was scored according to an analogue visual scale of difficulty from 0=None to 100=Severe. The total score was obtained by adding the scores of the 17 items of the subscale (range 0 – 1700). Missing data were managed in accordance with the WOMAC user guide [294].

Quality of life was assessed by the Assessment of Quality of Life instrument *(*AQoL) [295]. This generic multi-attribute instrument has 5 subscales (illness, independent living, social relationships, physical senses and psychological well-being) containing three items per subscale and four potential responses per item (each item scored 1-4). It has high reliability and validity (intraclass correlation coefficient (ICC) > 0.76) in population-based settings, including for older adult populations [332, 333]. The AQoL-4D used in this analysis is an indexed health utility score derived by scaling the scores of items 4-15 of the instrument (the illness subscale was excluded from the analysis as per the instrument scaling protocol [334]), and ranges from 1.0 (best) to -0.04 (worst), with negative scores indicating a health state worse than death [295]. The scores for each subscale ranged from 3-12, with higher scores indicating poorer quality of life.

7.3.3 Trunk muscle morphology

Abdominal and MF muscles were assessed using ultrasound imaging. A detailed description of the processes of image capture and measuring of abdominal and MF muscle thickness and MF cross-sectional area (CSA), as well test-retest reliability has previously been published [335]. In brief, ultrasound images were obtained using a Phillips HDI 5000 diagnostic ultrasound machine (Bothwell, WA, USA) in brightness mode (B-mode) with a handheld C7-4 (4-7 MHz) broadband curved array transducer. The ultrasound imaging (USI) was conducted by a physiotherapist trained in USI. Images were stored and later measured offline by a single examiner using Image J software, version IJ 1.36B, http://imagej.nih.gov/ij/). ICC for abdominal and MF muscle measurements were ICC= 0.74-0.98 for test-retest reliability [335].

Transverse images of the abdominal muscles were obtained with participants positioned in a supine position with a pillow positioned under their knees [121, 298]. The RA muscle was imaged at rest and images of the TrA, IO and EO were obtained at rest and contracted. Thickness of the abdominal muscles was measured as the perpendicular distance between the superior and inferior hyperechoic muscle fascias at approximately the middle of the image identified using the software's Cartesian coordinates [298].

Imaging of the MF muscles was carried out with participants lying prone with a pillow under their abdomen to reduce lumbar lordosis [122, 301, 317]. Transverse images of the MF muscle were obtained at rest and parasagittal images were obtained both at rest and during muscle contraction, for which participants were directed to "take a relaxed breath in and out, hold your breath out and try to slowly "swell" and contract the muscle without moving the spine" [174]. CSA of the MF muscle was measured by tracing around the inner edge of the fascial boundaries of the muscle [122, 315] and thickness was measured from the tip of the zygapophyseal joint to the inferior fascial edge of the superior border of the muscle [301].

7.3.4 Anthropometric characteristics

Height was measured by stadiometer to the nearest 0.1 cm (Leicester Height Measure, Invicta Plastics Ltd, Leicester, UK) and weight by calibrated scales (Heine S-7307, Heine, New Hampshire, USA). Body mass index (BMI) was calculated (weight (kg)/height ($m^{2)}$).

7.3.5 Statistical analysis

Correlational analysis was used to estimate cross-sectional associations between abdominal and MF muscle thickness and MF CSA in the relaxed state, and muscle function (assessed by changes in muscle thickness on contraction) and four outcome factors: self-reported physical activity, ambulatory physical activity, WOMAC functional deficit score [294] and quality of life (AQoL) [295, 336]. Because there were no statistically significant differences between the two sides, the means of the right and left muscle sizes were used in the analysis. The cross-sectional correlations between muscle size and physical activity and function did not differ systematically between the vitamin D and placebo groups (data not shown) so the data from the two treatment groups was pooled for these analyses. The results are reported as rank correlation coefficients adjusted for age, sex and body mass index (BMI).

To assess the impact of knee pain and physical dysfunction on the outcomes, correlational analysis was used to estimate cross-sectional associations between the WOMAC pain scores and four outcome factors: self-reported physical activity using IPAQ [293], ambulatory physical activity, physical dysfunction (WOMAC subscale score) and quality of life (AQoL) [295, 336]. Additionally, correlational analysis was used to estimate cross-sectional associations between the WOMAC pain and physical dysfunction subscales, and their associations with the measures of abdominal and MF muscle thickness and MF CSA. Finally, cross-sectional associations between abdominal and MF muscle thickness and MF CSA in the relaxed state, and the four

outcome factors were adjusted by knee pain scores. We also report the correlations of self-reported physical activity using IPAQ, ambulatory physical activity and quality of life (AQoL) with the muscle measures adjusted for physical dysfunction.

7.4 Results

Table 1 summarises the characteristics of participants. Of 217 participants, 48% were women. Women had higher average VAS scores for knee pain and functional deficit scores, but lower steps per day (7543 for men and 7300 for women respectively) and lower utility scores (AQoL-4D) (0.780 for men and 0.715 for women, respectively). There were no baseline differences in age, sex, anthropometric measures or vitamin D status between the participants in this sub-study and the entire VIDEO cohort (n=413) [292].

After adjusting for age, sex and BMI, all correlations between muscle size or function and measures of physical activity, physical function and quality of life were small (-0.173 – 0.099) and not statistically significant (Table 2 and 3). Other than an isolated instance (MET/hour/week and sex) among 48 tested, p-values for interaction by age or sex were greater than 0.1 (data not shown).

Severity of knee pain measured using the WOMAC subscale scores [294] was not associated with physical activity measured using IPAQ (rank correlation adjusted for sex, age and BMI = –0.056) or with ambulatory activity measured using pedometers (rank correlation adjusted for sex, age and BMI = –0.017). It was associated with physical dysfunction measured by the WOMAC subscale (rank correlation adjusted for sex, age and BMI= 0.808) and with quality of life measured by AQOL (rank correlation adjusted for sex, age and BMI = –0.295, $p<0.001$) (Table 2). However, severity of knee pain was only weakly associated with trunk muscle size or activation (rank correlations adjusted for sex, age and BMI: -0.052 – 0.049). In consequence, it was not necessary to adjust the rank correlations of physical dysfunction and quality of life with muscle size for severity of knee pain because those adjustments produced only minor changes (data not shown). Similarly, physical dysfunction measured by the WOMAC subscale was associated with quality of life (rank correlation adjusted for sex, age and BMI = -0.354), but not with physical activity (rank correlation adjusted for sex, age and BMI = -0.085) or ambulatory activity (rank correlation adjusted for sex, age and BMI = -0.030), and adjusting the associations of quality of life with muscle measures for physical dysfunction produced changes of little

consequence.

7.5 Discussion

To our knowledge, this is the first study investigating associations between the morphology and function of key postural trunk muscles and physical activity, physical dysfunction and quality of life of active older adults. Correlations between abdominal and MF muscle size and measures of physical activity, physical function or quality of life were small and not statistically significant indicating that muscle size and function (as determined by the change in thickness with submaximal contraction), may not contribute to these outcomes in older adults. Other measures such as trunk muscle attenuation and strength may be more relevant for functional outcomes in older adults.

Our results are largely consistent with previous studies that have failed to demonstrate associations between abdominal and MF muscles and measures of physical function. In line with the findings in the present study, in a 3-year observational study of 1194 older adults, using computed tomography (CT) to assess abdominal and paraspinal muscles, CSA was not associated with tests used to assess physical function (p->0.05) (chair stands, timed standing balance, balance and 6 minute walk test (6MWT)) [145]. Using magnetic resonance imaging (MRI) to measure MF muscle CSA and fat infiltrations at the L5 spinal level, Sions et al. [146] examined associations with measures of physical function (SF-36 PFS score, TUG, gait speed and fast stair descent) in 106 community-dwelling adults (60 – 85 years) that included people with and without CLBP. Their results showed that people with CLBP had worse self-reported and performance-based physical function, and that increased MF muscle fat infiltrations was associated with worse physical function among older adults. They also reported no association between MF muscle size and self-reported or performance-based physical function on older adults with or without CLBP. Despite the encouraging results from Shahtahmassebi et al [313], the results from previous studies and the current study suggest that neither abdominal or MF muscle size are associated with measures of physical activity, physical function or quality of life in older adults.

In the present study, there was no association between abdominal and MF muscle size or ability to contract these muscles and the ambulatory activity level (steps/day) of the participants, even when knee pain was included as a potential confounder. Walking has many identified health benefits for older adults that include prevention of cardiovascular disease, control of blood glucose, reduction in risk of cognitive impairment and increased social interaction [337]. Similar

to the findings in the present study, a 15-year observational study of monozygotic twins, reported that despite age-related decreases in MF and erector spinae muscle size, measured by MRI, there were no associations between levels of physical activity at work or leisure and changes in MF muscle size [268]. Similarly, in a study of 281 adults aged 61-71 years, Azuma et al. [167] reported that paraspinal muscle CSA was not associated with habitual exercise (exercising for at least 30 minutes per session, at least twice per week, for at least 1 year). Despite the health benefits of walking described above, there may be other elements such as increased exercise intensity, resistance exercises or weight bearing exercises that along with walking would be important to integrate in rehabilitation programs aiming to preserve abdominal and MF muscle size or function.

In contrast to our findings for abdominal and MF muscle size, there is evidence that other properties of trunk muscle such as composition (fat infiltrations) and strength are associated with measures of balance and physical function. Cross-sectional and longitudinal studies have reported that increased fat infiltrations in abdominal and paraspinal muscles was associated with poorer physical function (slower gait speeds, reduced TUG and stair descent performance) [146] and was a predictor of poorer functional function over three years [145]. Other studies have reported significant, positive associations between trunk muscle strength and measures of physical function, including the 30-second Chair Stand Test, the Sitting and Rising Test, the 6-minute walk time test, Berg Balance Scale [313], Unipedal Stance Test and SPPB [7] and balance [338, 339]. These studies included community-dwelling participants such as the ones in this study, and suggest that attributes of abdominal and MF muscles other than size, such as muscle composition and strength may be more relevant factors when investigating balance and physical function in older adults.

One of the strengths of this study was the use of objective measures of physical activity i.e. pedometer, rather than subjective measures only, which are often overstated [327, 340, 341]. Data are also presented on abdominal and MF muscle size at L2-L5 lumbar spine levels from 217 active older adults aged 50-79 (mean 63.3) years. This study also has some limitations. The participants were independent community-dwelling adults but with knee osteoarthritis and mild to moderate knee pain. Knee osteoarthritis is a common chronic joint disease [342] that is highly prevalent in older adults [343, 344], causes disability and pain and has the potential to influence physical activity and quality of life. However, the average knee pain levels for the participants in this study were relatively low, the participants were active (average steps per day >7300) and the average quality of life scores were in the high range. Consequently, the results from this study could, with

caution, be generalised to other older adults. It is important to note that the subscale of the WOMAC questionnaire used in this study is specifically designed for people with knee osteoarthritis to assess their perceptions of the effects of their knee on physical functions , such as managing stairs, ambulating and some activities of daily living (ADLs). Thus, while we can say that in people with moderately painful OA, size and activation of the trunk muscles measured are not associated with their perceptions of how their knee affects their physical function, further investigation is required before ruling out any association between trunk muscle size and activation and physical function more generally. It is possible that participants' physical function would have been affected, but not related to knee pain, which could have caused underreporting of limitations and could have affected our results. It may also be possible that the associations between muscles of the trunk and physical function could have differed if a tool specifically designed to assess physical function e.g. SPPB had been used. Finally, the participants in this study had low serum vitamin D levels which could affect physical function and may conceal any relationship between physical function and muscle size.

The current study contributes to a limited body of knowledge on the associations between abdominal and MF muscle size and measures of physical activity, physical function and quality of life, specifically in active adults aged 50-79 years. Although our results indicate a lack of association between abdominal and MF muscle size and function and measures of physical activity, physical function and quality of life, these should be interpreted within the limitations of the measures used to assess muscle function and physical function. Future studies should examine what other factors affect trunk muscles of older adults, the long-term effects of declines in muscle size on physical activity, physical function and quality of life of older adults and potential intervention strategies that can be implemented to mitigate the effect of age-related changes on these muscles.

Table 1. Characteristics of participants

	Males	Females
Sex % (n/N)	52.1 (113/217)	47.9 (104/217)
Age (yrs.)	63.7 (7.3)	62.0 (7.2)
Weight (kg)	90.8 (12.5)	77.5 (15.0)
Height (cm)	176.3 (6.4)	161.2 (6.5)
BMI (kg/m^2)	29.2 (3.8)	30.0 (5.8)
Vitamin D (nmol/L)	44.4 (11.5)	41.9 (12.5)
Current back pain %(n/N)	31.0 (35/113)	29.0 (30/104)
VAS score for current low back pain‡	32.1 (18.6)	32.0 (25.1)
WOMAC score for knee pain (0-500)	113.3 (81.5)	131.5 (90.4)
Mean muscle thickness (cm)†		
RA (cm)	0.91 (0.17)	0.76 (0.18)
TrA muscle thickness	0.44 (0.1)	0.34 (0.1)
IO muscle thickness	0.91 (0.26)	0.71 (0.18)
EO muscle thickness	0.46 (0.12)	0.42 (0.12)
Multifidus muscle thickness (L2-L3)	2.86 (0.45)	2.41 (0.38)
Multifidus muscle thickness (L3/L4)	2.53 (0.38)	2.11 (0.48)
Multifidus muscle thickness (L4/L5)	3.06 (0.45)	2.69 (0.51)
Multifidus muscle thickness (L5/S1)	2.95 (0.41)	2.52 (0.52)
Mean multifidus CSA (cm^2)†		
L2	2.82 (0.48)	2.47 (0.52)
L3	3.64 (0.52)	3.26 (0.61)
L4	4.47 (0.58)	4.15 (0.72)

L5	5.31 (0.74)	4.83 (0.88)
MET-hour-week (IPAQ)	67.3 (68.5)	43.0 (62.0)
Steps per day (Pedometer)	7542.6 (3049.6)	7300.4 (3320.2)
Functional deficit score (WOMAC) (ranges 0-1700)	370.7 (272.8)	424.4 (286.4)
Quality of life (AQoL-4D utility score) (ranges -0.04*=worst to 1=best)	0.780 (0.2)	0.715 (0.2)

All results reported mean (standard deviation) or % (n/N) where indicated. *BMI:* body mass index. ‡*VAS*: visual analogue scale (0-10 where 0=no pain and 10=very worst pain). † because there were no statistically significant differences between the two sides, the means of the right and left muscle sizes were used in the analysis. RA: rectus abdominis muscle, lateral abdominals: transversus abdominis, internal oblique and external oblique muscles, CSA: cross-sectional area, IPAQ: International Physical Activity Questionnaire, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index. AQoL The Assessment of Quality of Life instrument; utility scores scale from 1.0 (best) to -0.04 (worst)

Table 2. Cross-sectional correlations between abdominal and multifidus muscles in the relaxed state and physical activity, ambulatory activity, physical function and quality of life of adults 50-79 years of age.

Rank correlations adjusted for sex (male/female), age (years) and BMI (kg/m^2)				
	Physical activity (IPAQ)	**Ambulatory activity (Pedometer)**	**Physical dysfunction (WOMAC)**	**Quality of life (AQoL)**
Abdominal muscles thickness in relaxed state				
RA	0.099	0.01	-0.02	-0.075
TrA	-0.017	0.094	0.022	-0.056
IO	0.035	0.026	0.088	-0.071
EO	-0.066	-0.005	0.029	0.033
Multifidus muscle thickness in relaxed state				
L2/L3	0.012	-0.046	0.034	0.005
L3/L4	-0.043	-0.129	0.101	0.014
L4/L5	-0.05	-0.115	0.055	0.057
L5/S1	-0.02	-0.087	0.054	0.07
Multifidus muscle cross-sectional area in relaxed state				
L2	0.093	0.06	-0.039	-0.062
L3	0.064	-0.015	-0.126	-0.072
L4	0.007	0.000	-0.044	-0.115
L5	-0.04	-0.021	0.041	-0.173

Abbreviations: IPAQ, International Physical Activity Questionnaire; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; AQoL, The Assessment of Quality of Life instrument; *RA,* rectus abdominis; Lateral abdominals, transversus abdominis, internal oblique and external oblique muscles; * indicates statistically significant $p<0.05$; muscle sizes used in the models were averages of sides.

Table 3. Cross-sectional correlations between change in thickness with sub-maximal contraction (muscle function) of abdominal and multifidus muscles and physical activity, ambulatory activity, physical function and quality of life of adults 50-79 years of age.

Rank correlations adjusted for sex (male/female), age (years) and BMI (kg/m^2)				
	Physical activity (IPAQ)	**Ambulatory activity (Pedometer)**	**Physical dysfunction (WOMAC)**	**Quality of life (AQoL)**
TrA	-0.065	0.016	-0.048	-0.055
IO	-0.083	-0.022	-0.052	-0.111
EO	0.045	-0.006	-0.014	0.013
L2/L3_MF	-0.042	-0.092	0.049	0.072
L3/L4_MF	-0.034	-0.024	0.063	0.002
L4/L5_MF	-0.061	0.018	0.086	-0.034
L5/S1_MF	0.033	0.055	0.037	-0.034

Abbreviations: IPAQ, International Physical Activity Questionnaire; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; AQoL, The Assessment of Quality of Life instrument; *RA,* rectus abdominis; Lateral abdominals, transversus abdominis, internal oblique and external oblique muscles; * indicates statistically significant $p<0.05$; muscle sizes used in the models were averages of sides.

CHAPTER 8 – SUMMARY, FUTURE DIRECTIONS AND CONCLUSION

8.1 Background and aims of the thesis

By 2050, the global population of people aged 60 years and over will double, and the number of people over 80 years will triple [1]. This will have profound consequences on social-support systems and health budgets [2]. As the number of people aged 50 years and older increases, the number of people in the workforce within this age bracket is likely to increase as well. [345]. Therefore, it is important to identify factors that have the potential to affect healthy ageing and implement strategies that would increase the likelihood of maintaining the physical capacity for work and activities of daily living of people 50 years and over to enable this population to continue their participation in the workforce and enjoy a healthy ageing process. The muscles of the trunk have the potential to play a key role in maintaining older adults' physical capacity due to the complex role these muscles play in load transfer from the upper limbs to the pelvis, force dissipation, control of balance and posture, and movement of the trunk and pelvis [6, 8, 9]. Therefore, it is essential to have a good understanding of possible causes of decline in the size and function of the muscles of the trunk, and how such declines could potentially affect people's physical capacity and limit their quality of life.

8.1.1 Aims

It is well known that upper and lower limb muscles decrease in size and strength with increasing age. Both have been shown to be associated with decreases in physical function and quality of life of older adults. Among young adults, it has been shown that decreased muscle size and changes in activation of the abdominal and MF muscles are associated with LBP. However, there is little information regarding the changes in size that muscles of the trunk undergo with age and the effect these changes may have on the physical functioning of older adults. Therefore, the overarching aim of this thesis was to improve knowledge and understanding of the muscles of the trunk in older adults.

The specific aims of this thesis were: (1) to identify factors that affect the morphology, composition and function of the muscles of the trunk, (2) to ascertain whether a therapeutic intervention that has long been suggested for this population would have an effect on the size and function of these muscles, and (3) to ascertain whether age-related changes in the size of these muscles affect the physical activity levels, physical function and quality of life of older adults. In order to address the specific aims, a study was undertaken to investigate whether the reliability of USI as a tool to measure the size of these muscles in older adults was adequate for its use in clinical and epidemiology research addressing aims (2) and (3).

8.2 Key findings, limitations and future directions

In order to ascertain what was known about muscles of the trunk in older adults, a systematic review was undertaken. Chapter 3 of this thesis provided a comprehensive and systematic assessment of the current literature investigating abdominal and multifidus muscle in adults aged 50 years and older. The results from the systematic review in Chapter 3 confirmed that there was a paucity of information available on the therapeutic benefits of vitamin D supplementation on muscles of the trunk and that little was known about the role these muscles play in the physical functioning and quality of life of older adults. It also reinforced the need to undertake further reliability studies to ascertain the reliability and validity of USI as a tool to measure the size of abdominal and MF muscles. Chapters 5-7 addressed the second and third parts of the aims of this research project and filled important gaps in the literature identified in the systematic review. Studies in Chapters 5 - 7 used data from an ultrasound imaging sub-study (n=217) of the Vitamin D Effect on Osteoarthritis (VIDEO) clinical trial, conducted between June 2010 and December 2013. The participants were community-dwelling adults aged 50-79 years with ongoing symptoms of knee osteoarthritis and serum 25(OH)D levels between 12.5 and 60 nmol/L.

8.2.1 Key findings

The systematic review in Chapter 3 showed that size, strength, activation and quality of the muscles of the trunk could be influenced by ageing, spinal conditions, LBP, stroke or decreased physical activity. In the remainder of this project, it was decided to focus attention on the size of the abdominal and MF muscles as important muscles of the trunk. This was an important consideration because it enabled focus on the specific characteristics of individual muscles. Other aspects of muscle function such as strength and power were not considered because the measurements cannot be made for individual muscles. Trunk muscle activation was also not investigated because the studies that used EMG to measure trunk muscles of older adults were conflicting. The assessment of muscle composition requires expensive equipment.

One of the gaps in the literature identified in the systematic review was a lack of information about the test-retest of measurements of trunk muscle size using USI in older adults. This prompted undertaking of a test-retest reliability study of USI for the assessment of abdominal and MF muscle thickness and CSA in adults aged 50-79 years (Chapter 5). The results showed moderate to substantial reliability for the majority of muscles measured and confirmed the appropriateness of using these measures in longitudinal studies and as outcomes for RCTs.

Having established that USI was a reliable tool to measure abdominal and MF muscles size, USI was used to fill another gap in the literature identified in the systematic review by investigating a potential cost-effective intervention for the maintenance of abdominal and MF muscles. Vitamin D supplementation has long been mooted as a therapeutic intervention for skeletal muscle, but no studies were found on its efficacy for abdominal or MF muscles. Chapter 3 presented a study investigating the effect of vitamin D supplementation on abdominal and MF muscles in vitamin D deficient adults 50 - 79 years. This study provided robust evidence for a lack of effect of vitamin D supplementation on the size or function of the abdominal and MF muscles of older adults, hence informing clinicians treating patients affected by the effects of vitamin D deficiency that vitamin D supplementation alone is not an effective therapy to improve or preserve the size, or ability to contract of these postural muscles of the trunk. Future vitamin D trials need to focus instead on measures of trunk muscle strength and fat infiltrations. This is because the literature on the effect of vitamin D on skeletal muscle is conflicting [216, 311] and recent studies indicate that changes in trunk muscle strength and fat infiltrations appear to be an important determinant of physical function of older adults [7, 313, 338, 339].

A further gap in the literature was the limited number of studies investigating associations between muscles of the trunk and measures of physical activity, physical function or quality of life, particularly in healthy older adults. This prompted the investigation of associations between abdominal and multifidus muscle size and function (assessed by changes in muscle thickness on contraction) and measures of physical activity, physical function and quality of life among healthy, community-dwelling adults aged 50-79 years with knee osteoarthritis (Chapter 7). This study revealed only weak cross-sectional correlations between abdominal or MF muscle size or function and measures of physical activity, functional deficit subscale of the WOMAC or quality of life. Despite the limitations, the findings in this study are consistent with current literature [145, 279] indicating that muscle size may not be an important determinant of physical activity, physical function or have an impact on older adult's quality of life. Therefore, these findings inform both clinicians designing rehabilitation programs for older adults and future research in the area.

Finally, the systematic review update (second part of Chapter 3) included several studies that filled some of the gaps identified in the systematic review. These included studies examining the validity and reliability for the assessment abdominal and MF muscles using imaging techniques and importantly, studies investigating associations between trunk muscle morphology and quality and measures of physical function. The latter studies suggest that abdominal and MF

muscle strength and muscle quality are important determinants of physical function in older adults. Therefore, these factors would appear to be promising directions for future research investigating the effect of age-related changes in abdominal and MF muscles on physical function and quality of life of older adults.

8.2.2 Strengths and limitations

Collectively, the findings within this thesis have contributed to the limited knowledge-base on the abdominal and MF muscles in older adults by identifying and addressing some critical gaps in the literature. This thesis followed a systematic approach to the collection of information and provided a summary of the current literature on abdominal and MF muscles. The double-blind RCT design of the study in Chapter 6 provided robust evidence regarding the efficacy of vitamin D supplementation for improving or maintain trunk muscle size. Lastly, the use of objective measures of physical activity and the use of a highly reliable and valid instrument to measure quality of life added strength to the findings in Chapter 7. However, the findings from the studies in this thesis should be interpreted within the context of their limitations.

In relation to the systematic review, the focus was on studies that used EMG and imaging techniques to assess muscles individually. Therefore, studies that used other methods of assessing trunk muscle structure or function were not included. The study in Chapter 7 has several important limitations, including the cross-sectional design that does not allow inferences about causation to be drawn. The indicator of muscle function used, was change in muscle thickness with contraction, and hence it was not possible to tell if other aspects of muscle function may have been affected by vitamin D supplementation. The measure of physical function was part of a questionnaire tailored to assess the effects of knee OA on physical function and thus has an emphasis on activities that involve primarily the use of the lower limbs, and not specifically muscles of the trunk.

8.2.3 Future directions

In compiling this thesis, several directions for future research have become evident and are outlined below:

- Longitudinal studies investigating the effect of potential age-related factors that can affect muscles of the trunk and the effect of pathological conditions. These studies will inform the development of strategies to counteract any detrimental effect of those factors on muscles of the trunk.

- Longitudinal studies investigating association between trunk muscle morphology, strength or fat infiltrations and measures of physical activity, physical function or quality of life.
- Studies investigating cost-effective interventions that would help individuals mitigate the effects of ageing or pathology on muscles of the trunk.
- Longitudinal studies investigating the effect of vitamin D supplementation on trunk muscle size, strength or fat infiltrations, for people with severe vitamin D deficiency or for people with restricted mobility. These studies would inform clinicians about potential cost-effective therapies for people affected by vitamin D deficiency.

8.3 Conclusion

In conclusion, the information presented in this thesis has shown that age and various spinal conditions, LBP and stroke have detrimental effects on abdominal and MF muscle size, strength, activation and muscle quality, reflected in an increase in intramuscular fat infiltrations. The analysis of data from a USI sub-study of a clinical trial demonstrated that in active, community-dwelling adults aged 50 to 79 years with low serum vitamin D levels and knee osteoarthritis, abdominal or MF muscles size may not be an important determinant of physical capacity outcomes. The effect of strength and intramuscular fat infiltrations on muscles of the trunk appear to be promising directions for future research when investigating the effect of age-related changes in abdominal and MF muscles on physical function and quality of life of older adults.

CHAPTER 9 - REFERENCES

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CHAPTER 10 - APPENDICES

Appendix 1: Vitamin D supplementation in the management of knee osteoarthritis: study protocol for a randomized controlled trial

Cao *et al. Trials* 2012, **13**:131
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TRIALS

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Vitamin D supplementation in the management of knee osteoarthritis: study protocol for a randomized controlled trial

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Abstract

Background: Osteoarthritis (OA) is a common health issue worldwide in the aging population who are also commonly deficient in vitamin D. Our previous study suggested that higher serum 25-(OH)D levels were associated with reduced knee cartilage loss, implying that vitamin D supplementation may prevent the progression of knee OA. The aim of the Vitamin D Effects on OA (VIDEO) study is to compare, over a 2- year period, the effects of vitamin D supplementation versus placebo on knee structural changes, knee pain, and lower limb muscle strength in patients with symptomatic knee OA.

Methods/design: Randomised, placebo-controlled, and double-blind clinical trial aiming to recruit 400 subjects (200 from Tasmania and 200 from Victoria) with both symptomatic knee OA and vitamin D deficiency (serum [25-(OH)D] level of >12.5 nmol/liter and <60 nmol/liter). Participants will be randomly allocated to vitamin D supplementation (50,000 IU compounded vitamin D_3 capsule monthly) or identical inert placebo group for 2 years. The primary endpoint is loss of knee cartilage volume measured by magnetic resonance imaging (MRI) and Western Ontario and McMaster Universities Index of OA (WOMAC) knee pain score. The secondary endpoints will be other knee structural changes, and lower limb muscle strength. Several other outcome measures including core muscle images and central blood pressure will be recorded. Linear and logistic regression will be used to compare changes between groups using univariable and multivariable modeling analyses. Both intention to treat and per protocol analyses will be utilized.

Discussion: The trial is designed to test if vitamin D supplementation will reduce loss of knee cartilage volume, prevent the progression of other knee structural abnormalities, reduce knee pain and strengthen lower limb muscle strength, thus modify disease progression in knee OA.

Trial registration: ClinicalTrials.gov identifier: NCT01176344; Australian New Zealand Clinical Trials Registry: ACTRN12610000495022

Keywords: Vitamin D, Osteoarthritis, Magnetic resonance imaging

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Cao et al. Trials 2012, 13:131
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Background

Osteoarthritis (OA) is the most common form of arthritis in the world and one of the most common chronic conditions managed in Australian general practice [1,2]. It is characterized by the gradual loss of articular cartilage and changes to other joint structures eventually leading to total joint replacement. Currently there is no cure for OA, and the development of innovative and cost-effective approaches to prevent the development and progression of OA is urgent and important.

Vitamin D comprises a group of fat-soluble secosteroids emcompassing two major molecules, vitamin D_2 and vitamin D_3. Vitamin D is circulated to the liver where it is converted to the prohormone calcidiol, or 25-hydroxy-vitamin D (25-(OH)D), which is the best indicator of vitamin D status [3-5]. Vitamin D deficiency is very common in older people. It is estimated that 20 to 100% of elderly men and women in North America and Europe are vitamin D deficient (mostly defined as a serum level of 25-(OH)D < 50 nmol/liter)[6,7]. High rates of vitamin D deficiency have also been reported in all sectors of the community of Australia, especially in Tasmania and Victoria where this study will be conducted [8-10].

It has been widely recognized that OA is a disease affecting the whole joint, including cartilage, bone and muscle. Through targeting these joint tissues vitamin D supplementation may modify disease progression in OA. Vitamin D receptors (VDRs) are found in human articular chondrocytes [11], and 1α-25$(OH)_2D_3$ regulates the expression of metalloproteinase (MMP) and prostaglandin E_2 (PGE_2) in chondrocytes via VDRs [11]. Vitamin D could enhance the ability of bone to respond optimally to pathophysiological processes in OA, thus prevent disease progression [12,13]. Furthermore, 1,25$(OH)_2D$ leads to *de novo* protein synthesis, muscle cell growth, and improved muscle function, and thus has a beneficial effect on muscle strength [14].

Epidemiological studies have provided preliminary evidence supporting the potential use of vitamin D for the treatment of OA. Lower serum levels of 25-(OH)D were associated with greater knee pain [15] and higher prevalence of radiographic OA [16], and predicted incidence of knee pain [17], progression/incidence of radiographic OA [18,19], and loss of joint space, as well as osteophyte growth [18]. Magnetic resonance imaging (MRI) has been utilized to directly assess knee structural alterations such as cartilage volume, cartilage defects, subchondral bone changes and meniscal lesions. Using MRI, we reported that, in cross-sectional analysis, serum 25-(OH)D level was significantly and positively associated with knee cartilage volume in older men and women, and vitamin D insufficiency was positively associated with medial and lateral tibial bone area in women. Longitudinally, higher baseline serum levels of 25-(OH)D predicted reduced loss of cartilage volume over 2 years, and increases in vitamin D levels were associated with further protective association [15,16]. Furthermore, serum levels of 25-(OH)D were also associated with increased leg muscle strength and quality, and thus may be important for the maintenance of muscle function [20].

Based on this experimental and epidemiological evidence, we have initiated a randomized, placebo-controlled trial (Vitamin D Effect on Osteoarthritis, VIDEO study) to determine if vitamin D supplementation can reduce loss of knee cartilage volume, prevent the progression of other knee structural abnormalities and strengthen lower limb muscle strength, and thus modify disease progression in knee OA. The effects of vitamin D supplementation on the progression of knee pain will also be determined.

In a sub-study, we will examine the effects of vitamin D supplementation on the function of deep lumbo-pelvic stabilising muscles. The protective deep lumbo-pelvic stabilising muscles, which include (but not exclusively) the transversus abdominus (TrAb) and lumbar multifidus and which are known as core muscles, become dysfunctional shortly after the onset of low back pain, and that ongoing muscle dysfunction is associated with persistent low back pain [18,21]. Muscle weakness can be a sign of vitamin D deficiency [19] and therefore, vitamin D supplementation may have beneficial effects on functionally important core muscles.

Furthermore, we will determine the effect of vitamin D supplementation on blood pressure (clinical, ambulatory, upper arm and central measures) and arterial stiffness (aortic pulse wave velocity). Several lines of evidence suggest that vitamin D deficiency may influence blood pressure via mechanisms including activation of the renin-angiotensin-aldosterone system (RAAS) [22-24]. Central and ambulatory blood pressure will be the main outcomes because central blood pressure is the actual pressure load experienced by the heart (and other organs such as the kidneys and brain) rather than the pressure at the upper arm [25], and ambulatory blood pressure is regarded as the gold standard technique because it correlates with target organ damage and provides more accurate information on daily (including night time) blood pressure fluctuations [26].

Methods/design

Study design

VIDEO is a randomized, placebo-controlled double-blind clinical trial. Four hundred subjects (200 from Tasmania and 200 from Victoria) with symptomatic knee OA and serum 25-(OH)D > 12.5 nmol/liter and < 60 nmol/liter will be recruited and randomly allocated to either the

Cao et al. Trials 2012, 13:131
http://www.trialsjournal.com/content/13/1/131

treatment or placebo control group. Recruitment methods will include advertisements through the local media and community groups as well as liaisons with general practitioners, specialist rheumatologists, and orthopedic surgeons. Ethics approval has been received from The Tasmania Health and Human Medical Research Ethics Committee (reference number H1040) and Monash University Human Research Ethics Committee (reference number CF10/1182 - 2010000616). Informed written consent will be obtained from all participants.

Inclusion criteria

The inclusion criteria were as follows: age 50 to 79 years; symptomatic knee OA for at least 6 months with a pain at least 20 mm on a 100 mm visual analogue scale (VAS); American College of Rheumatology (ACR) criteria for symptomatic knee OA assessed by a rheumatologist [27]; ACR functional class rating of I, II and III [28]; relatively good health, with a score of 0 to 2 on a 5-point Likert scale (with a range of 0 indicating very good health to 4 indicating very poor health), according to the investigators global assessment of disease status; serum 25-(OHD)D > 12.5 nmol/liter and < 60 nmol/liter; able to read, speak and understand English, capable of understanding the study requirements and willing to cooperate with the study instructions.

Exclusion criteria

Exclusion criteria were as follows: severe radiographic knee OA, grade 3 according to Altman's atlas [29]; severe knee pain on standing (more than 80 mm on 100-mm VAS); any contraindication to having MRI; rheumatoid or psoriatic arthritis, lupus or cancer; severe cardiac or renal impairment; hypersensitivity to vitamin D; any condition possibly affecting oral drug absorption (for example, gastrectomy or malabsorption syndromes); significant trauma to knees, including arthroscopy or significant injury to ligaments or menisci of the knee within one preceding the study; anticipated need for knee or hip surgery within the next 2 years; history of taking vitamin D supplements within the previous 30 days; history of taking an investigational drug within the previous 30 days.

Randomization

Participants in each site will be randomly assigned to the intervention arm or placebo arm in a ratio of 1:1 and the randomization will be double-blind. Allocation of participants will be based on computer-generated random numbers. Allocation concealment will be ensured by the use of an identical inert placebo, and a central automated allocation procedure, with security in place to ensure allocation data cannot be accessed or influenced by any person.

Intervention

Participants in the intervention arm will take one capsule per month of 50,000 IU (1.25 mg) of a vitamin D3 compound (cholecalciferol), purchased from Nationwide Compounding Pharmacy, Melbourne, Australia[30], and patients in the control arm will receive an identical inert placebo provided by the same company. Patients are required to record their medication information in personal diaries and a reminder will be given each month. All participants will receive the recommended standard of care. The duration of the study is 2 years.

Quality assurance

To ensure that this trial will be of a high standard and delivered in accordance with the trial protocol, all research staff will be provided with a standard protocol and case report form, and will be trained to competently administer items as per protocol. The investigators, research assistants and outcome assessors are different people. Protocols will not be altered during the study timeframe.

Outcome measures

The co-primary efficacy endpoints of the study will be MRI assessment of volume changes in knee cartilage from baseline to month 24, as well as the Western Ontario and McMaster Universities Index of OA (WOMAC) score [31] (Table 1). The secondary endpoints will be other knee structural changes (cartilage defects, tibial plateau bone area, and bone marrow lesions, meniscal tear and extrusion) from baseline to month 24, and lower limb muscle strength at months 3, 6, 12 and 24 (Table 1).

MRI assessment of knee structural changes

Knees will be imaged in the sagittal plane on a 1.5-T whole body MRI unit using a commercial transmit-receive extremity coil. Fat-saturated T1-weighted spoiled gradient echo (GRE) and T2-weighted/proton density-weighted fast spin echo (FSE) sequences will be used. The images will be assessed by two readers blinded to the treatment according to the methods described in our previous publications [15,32].

Cartilage volume: the volumes of individual cartilage plates (medial tibial, lateral tibial and patella) are isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. Sagittal images will be obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.31 mm (512×512 pixels), then resampled by means of bilinear and cubic interpolation (area of 312 μm × 312 μm and multiplied by 1.5 mm thickness, continuous sections) for the final 3D rendering. Particular cartilage volume was then determined by

Cao et al. Trials 2012, 13:131
http://www.trialsjournal.com/content/13/1/131

Table 1 Timetable and measures to be made

	Screening	Month(s)				
		0	3	6	12	24
Co-primary outcome measure						
MRI (cartilage volume changes)		✓				✓
WOMAC		✓	✓	✓	✓	✓
Secondary outcome measure						
MRI (other structural changes)		✓				✓
Lower limb muscle strength		✓	✓	✓	✓	✓
Other measures						
Core musculature measure		✓			✓	✓
Hand grip strength		✓	✓	✓	✓	✓
Central and upper arm blood pressure		✓		✓	✓	✓
Aortic stiffness		✓		✓	✓	✓
Physical activity (IPAQ)		✓				✓
Body fat		✓			✓	✓
Low foot pain		✓	✓	✓	✓	✓
Low back pain		✓		✓	✓	✓
Depression		✓	✓	✓	✓	✓
Quality of life		✓		✓	✓	✓
Previous knee injury and occupation		✓				✓
Weight		✓	✓	✓	✓	✓
Height		✓				✓
Girth measurements		✓			✓	✓
Knee radiograph	✓					
Serum 25-(OH)D	✓		✓			✓
Serum calcium, phosphate, creatinine	✓		✓			
Sun exposure		✓		✓	✓	✓
Cigarette smoking		✓				✓
Diet (FFQ) and pedometer		✓				✓
Medications	✓	✓	✓	✓	✓	✓
Pill counts and adverse events		✓	✓	✓	✓	✓

Participants who withdraw within one year will be asked to have MRI at month 12; patients who withdraw after one year will be asked to have MRI straight away. MRI: magnetic resonance imaging; WOMAC: Western Ontario McMaster Universities Osteoarthritis Index; 25-(OH)D: 25-hydroxy-vitamin D; FFQ: food frequency questionnaire.

summing all the pertinent voxels within the resultant binary volume.

Cartilage defects assessment: the cartilage defects (0 to 4) will be graded at medial tibial and femoral, lateral tibial and femoral, and patellar sites: grade 0, normal cartilage; grade 1, focal blistering and intracartilaginous low-signal intensity area with an intact surface and bottom; grade 2, irregularities on the surface or bottom and loss of thickness of less than 50%; grade 3, deep ulceration with loss of thickness of more than 50%; grade 4, full-thickness chondral wear with exposure of subchondral bone.

Knee tibial plateau bone area: the area of the medial and lateral tibial plateau bone will be measured manually on the three reformatted images closest to the tibial cartilage. An average of these three areas will be used as an estimate of the tibial plateau bone area.

Subchondral bone marrow lesions: This will be assessed on the T2-weighted MRI and defined as discrete areas of increased signal adjacent to the subcortical bone at the lateral, medial femur and/or tibia. Each bone marrow lesion will be scored on the basis of lesion size, for example, a lesion is scored as grade 1 if it occupies < 25% of the region; grade 2 if it occupies 25% to 50% of the region; or grade 3 if it occupies > 50% of the region.

Meniscal tear assessment: the menisci will be assessed in the sagittal view and confirmed in the coronal and axial views as previously described [33]. In brief, the presence or absence of a tear is based on the presence of a signal, which is line shaped, brighter than the dark meniscus, and reaches the surface of the meniscus at both ends within six defined regions (anterior horn, body, and posterior horn at both medial and lateral tibiofemoral compartments).

Mensical extrusion assessment: the extent of meniscal extrusion on the medial or lateral edges of the tibial femoral joint space for the anterior, body, and posterior horns of the menisci will be graded, where a score of 0 = no extrusion, 1 = partial meniscal extrusion, and 2 = complete meniscal extrusion with no contact with the joint space.

Lower limb muscle strength

This will be measured by dynamometry (TTM Muscle Meter, Tokyo, Japan) at the lower limb (involving both legs simultaneously). The muscles measured with this technique are mainly the quadriceps and hip flexors. The device will be calibrated by suspending known weights at regular intervals.

WOMAC

Knee pain will be assessed by both WOMAC pain subscale (walking on a flat surface, going up/down stairs, at night in the bed , sitting/lying and standing upright) and a 100 mm VAS.

Other measurements

Core musculature measure: Core muscle images will be taken at baseline and 12 months. Images of the core muscles (TrAb, internal oblique muscles and LM) are taken with real-time dynamic ultrasound using a fully featured big box diagnostic ultrasound machine (Phillips HDI 5000, Bothell, WA, US) with a hand held 7.5 mHz linear array transducer. Images are taken of right and left sides, both at rest and during contraction (drawing in of abdomen) using previously published protocols [34,35].

Cao et al. Trials 2012, 13:131
http://www.trialsjournal.com/content/13/1/131

These measures have a high degree of reliability with an interclass correlation coefficient (ICC) > 0.90 across a range of studies [36].

Upper arm blood pressure, central blood pressure and aortic stiffness: Clinical upper arm blood pressure will be measured twice after 5 minutes seated rest using a validated device (Omron HEM-907, Kyoto, Japan). Seated clinical central blood pressure will be recorded (immediately after upper arm blood pressure) using radial applanation tonometry (SphygmoCor 8.1, AtCor Medical, Sydney, Australia). Aortic stiffness will be measured by electrocardiogram-gated, sequential carotid to femoral pulse wave velocity as per expert consensus [37].

Physical activity: Physical activity will primarily be assessed using a pedometer (SW 200 Digi-Walker, Yamax Corporation, Tokyo, Japan), which measures vertical displacement (steps per day). The pedometer will be worn for seven consecutive days on two occasions (baseline and 2 years) as up to seven days is required to accurately assess habitual physical activity [38]. We will also measure physical activity using the International Physical Activity Questionnaire (IPAQ) short version [39].

Body fat: Body fat will be assessed using bioelectrical impedance analysis (BIA) (BIA analyser, Quantum II, RJL Systems, Michigan, USA). Fat-free mass, % fat-free mass, fat mass and % fat mass will be assessed [40].

Hand grip strength: Hand grip strength will be assessed to the nearest kg in both the right and left hand using a hydraulic hand dynamometer (Saehan Corporation, Masan, Korea). Both hands will be alternately measured in triplicate.

Radiographic OA: this will be assessed at baseline by a standing semiflexed anterior-posterior (AP) radiograph as per the Altman atlas [29]. Radiographs will also be assessed simultaneously by two observers using the Osteoarthritis Research Society International (OARSI) atlas to score osteophytes and joint space narrowing on a four-point scale (0 to 3).

Laboratory measurements: serum 25-(OH)D will be assayed at month 0, 3 and 24, utilizing a Liquid Phase radioimmunoassay (Immunodiagnostics Systems Ltd, Boldon, Tyne & Wear, UK). Serum calcium, phosphate and renal function will be assessed at month 0 and 3 using routine biochemical methods.

Anthropometrics and other questionnaires: Height will be measured to the nearest 0.1 cm (with shoes removed) using a stadiometer (Leicester Height Measure, Invicta Plastics Ltd, Leicester, UK). Weight will be measured to the nearest 0.1 kg (with shoes and bulky clothing removed) using electronic scales (Heine S-7307, Heine, New Hampshire, USA). Waist and hip measurements will be assessed using a tape measure to the nearest 0.1 cm (Figure Finder Tape Measure, Novel Products Inc, Illinois, USA). Sun exposure, employment status and occupation, depression, smoking status, previous knee injury, dietary intake, low back and foot pain and quality of life will be assessed by questionnaires.

Safety assessments

Spontaneously reported adverse events will be recorded throughout the study. Intensity and relationship with the study medication will be ascribed.

Sample size

All sample size calculations assume $\alpha = 0.05$ and $\beta = 0.20$ and are performed based upon formulae provided by Cohen [41]. Table 2 describes the sample size (each arm) needed to detect the specified differences between the placebo and vitamin D arms with at least 80% power for each outcome.

Previous studies, including our own, suggest that OA patients have a loss of cartilage volume of 4 to 5% per year at different joint sites, respectively [42]. Vitamin D supplementation in doses ranging from 400 to 800 IU/d increased the serum level of 25-(OH)D by 27 nmol/liter per year in 7,964 men and women from five studies [43]. We estimate from our published data [15] that this change will lead to absolute reduction in loss of cartilage volume by 2.2% at the medial tibial site after vitamin D supplementation. The sample size that is needed to detect this difference is calculated (Table 2).

We have shown that male OA patients have an increase in medial tibial bone area of 1.6 ± 2.8% per year [44], and an incidence of knee cartilage defects of 80% over 2 years [45]. There are no data known to the investigators about the associations between change in vitamin D and change in bone area or cartilage defects. However, healthy subjects have been shown to have an increase in tibial bone area of 0.7% per year (CD *et al.*, unpublished), and an incidence of knee cartilage defects of 65% over 2 years in older people [46]. Assuming that changes in cartilage defects and bone area in OA patients will be suppressed by vitamin D supplementation to the levels in the healthy subjects, the sample size needed to detect these differences is given in Table 2.

Table 2 Sample size calculation

	Mean (SD)	Detectable difference	Calculated sample size (per arm)
Loss of volume of medial tibial cartilage	4.5% ± 6.5%	2.16%	143
Increase in medial tibial bone area	1.6% ± 2.8%	0.9%	153
Incidence of knee cartilage defects	80%	15%	136

Cao et al. Trials 2012, 13:131
http://www.trialsjournal.com/content/13/1/131

Therefore, 200 patients in each arm (allowing for a 20% dropout over the trial) will be sufficient to detect the differences between treatment groups.

Analysis plan

Statistical primary comparisons for total and subscale WOMAC scores will be made using a repeated measures mixed model with terms for treatment, month, center and the corresponding baseline values as the covariates. The independent *t*-tests will be used to compare changes between groups in quantitative data from baseline to the end of follow-up. Linear regression (annual changes in cartilage volume, cartilage defects, bone area and muscle strength as the dependent variables, and treatment as the independent variable) and logistic regression (development/progression of bone marrow lesions and meniscal abnormalities as the dependent variables, treatment as the independent variable) analyses will be applied in univariate and multivariate modeling adjusted for age, sex, body mass index, baseline 25-(OH)D and other disease status.

In secondary analysis of loss in cartilage volume, the minimal clinically important differences (MCID) in cartilage volume will be calculated [47] and logistic regression will be used to determine the association between cartilage loss (> = MCID vs. < MCID) and treatment before and after adjustment for the covariates described above.

Both intention to treat and per protocol analyses will be utilized. Per protocol will be defined as achieving a 25-(OH)D level > 60 nmol/liter at month 3. The last observation carried forward method will be used in the analysis of all outcomes among patients who made at least one follow-up visit but did not complete the whole study.

Data integrity and management

All data obtained will be kept strictly confidential and will be stored electronically on a database with secured and restricted access. Data transfer will be encrypted and any information capable of identifying individuals will be removed.

Withdrawal

If a participant withdraws or is removed from the study, the reason and date of discontinuation will be recorded. Any participant who withdraws within year 1 will be asked to have MRI at the end of year 1; participants withdrawing after year 1 will be asked to have MRI on leaving the study.

Monitoring

The trial will be overseen and monitored by a project manager. The project manager will visit each site to examine trial procedures to ensure data quality and compliance with the trial protocol.

Discussion

We have proposed this protocol to determine if vitamin D supplementation can slow disease progression in patients with knee OA. Vitamin D may have beneficial effects for the treatment of OA, although there are currently no recommended guidelines for this approach [48]. Hence, well-designed randomized controlled trials are required to test if vitamin D has disease-modifying and pain-relieving effects. Such studies also need an appropriate follow-up period to capture joint structural changes using objective measurements over the course of OA, and this has been incorporated into the design of the VIDEO study.

Assessing disease-modifying effects on OA requires an accurate measurement tool that is able to evaluate improvements in cartilage and joint health. Radiographic assessment of OA is two-dimensional, lacks sensitivity for changes over a short period and is highly susceptible to measurement error through factors such as variation in joint positioning [49]. MRI allows direct, accurate and reliable assessment of joint structural changes over time. These structural changes include cartilage loss, cartilage defects, increased tibial bone area, subchondral bone marrow lesions, meniscal tears and meniscal extrusion. Almost all these structural changes are predictive of total knee replacement [45,50,51], suggesting they are clinically relevant. Simultaneously, we will assess change in knee pain over time using WOMAC as a co-primary endpoint. Thus, the findings from this study will show whether vitamin D supplementation has both disease-modifying and symptom-relieving effects.

As suggested by the 2011 Endocrine Society Clinical Practice Guideline, all adults aged 50 to 70 years, and those over 70 years old require at least 600 and 800 IU/d of vitamin D respectively, to maximize bone health and muscle function. To raise blood levels of 25-(OH)D above 75 nmol/liter (the lowest sufficient threshold) requires at least 1500 to 2000 IU/d of supplemental vitamin D [52]. Thus, our study design provides a dose of 50,000 IU monthly to achieve serum 25-(OH)D levels above 60 nmol/liter in all compliant subjects [53]. This method will be less costly and will be more convenient than daily treatment. Toxicity is extremely unlikely with this dose.

Two sub-studies will simultaneously be included in this trial. Firstly, we will examine the effects of vitamin D on the function of the deep lumbo-pelvic stabilizing muscles. Besides implications for low back pain, in healthy people core muscles have also been implicated in varying aspects of physical function. The lateral abdominal muscles are theorized to control movement and provide stability to the trunk for functional activities and this is supported in a number of studies [54]. Vitamin D supplementation may have beneficial effects on

functionally important core muscles. Secondly, we will determine the effect of vitamin D supplementation on blood pressure and aortic stiffness. A recent systematic review suggested that there is accumulating evidence to support the hypothesis that vitamin D deficiency contributes to hypertension, and randomized controlled trials (RCTs) are greatly needed to clarify and to definitively prove the effect of vitamin D on blood pressure [55]. The VIDEO study aims to be the first to assess this.

In summary, knee OA is a major, but poorly understood, public health problem. Vitamin D deficiency may play a role in the progression of OA, and based on our novel preliminary data, the VIDEO study has been designed to determine whether intervening with vitamin D supplementation can in fact slow the progression of this disease and relieve knee pain. If correcting vitamin D deficiency can reduce rates of cartilage loss to lower levels as seen in older people without OA, it will significantly prolong the time it takes to reach end-stage OA eventually requiring joint replacement. This suggests great potential for substantial cost savings through reductions in joint replacement surgery, as well as potential for great improvements in the quality of life for people with OA. The success of this study will provide scientific evidence for using a cost-effective and innovative approach to addressing this clinically significant problem and will lend itself to an easy public health intervention.

Trial status

Upon submission, VIDEO study is in the process of patient recruitment.

Abbreviations

25-(OH)D: 25-hydroxy-vitamin D; ACR: American College of Rheumatology; AQOL: assessment of quality of life; BIA: bioelectrical impedance analysis; CRF: case report form; FSEL: fast spin echo; FFQ: food frequency questionnaire; GRE: gradient echo; ICC: interclass correlation coefficient; IPAQ: International Physical Activity Questionnaire; LM: lumbar multifidus; MCID: minimal clinically important differences; MMP: metalloproteinase; MRI: magnetic resonance imaging; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; PHQ-9: Personal Health Questionnaire Depression Scale-9; PGE_2: prostaglandin E_2; RAAS: renin-angiotensin-aldosterone system; RCT: randomized controlled trial; SOP: standard operating procedure; TASOAC: Tasmania Older Adult Cohort; TrAb: transversus abdominus; VAS: visual analogue scales; VIDEO: Vitamin D Effects on Osteoarthritis; VDR: vitamin D receptors; WOMAC: Western Ontario McMaster Universities Osteoarthritis Index.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CD and GJ conceived the study, CD, GJ, FC, TW, AW, JS, KN and YC participated in its design and coordination, and performed the research. YC, GJ, KN and CD drafted the manuscript. All authors revised the manuscript and gave final approval of the version to be submitted.

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Appendix 2: International Physical Activity Questionnaire (PAQ)

International Physical Activity Questionnaire (IPAQ)
Short version

PLEASE ANSWER EACH QUESTION EVEN IF YOU DO NOT CONSIDER YOURSELF TO BE AN ACTIVE PERSON. THINK ABOUT THE ACTIVITIES YOU DO AT WORK, AS PART OF YOUR HOUSE AND YARD WORK, TO GET FROM PLACE TO PLACE, AND IN YOUR SPARE TIME FOR RECREATION, EXERCISE OR SPORT.

Think about all the *vigorous* activities which take *hard physical effort* that you did in the last 7 days. Vigorous activities make you breathe much harder than normal and may include heavy lifting, digging, aerobics, or fast bicycling. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities?
   _____ Days per week

   ☐ Don't Know/Not Sure

   ☐ Refused

   [**Interviewer clarification**: Think only about those physical activities that you do for at least 10 minutes at a time.]

   [**Interviewer note**: If respondent answers zero, refuses or does not know, skip to Question 16]

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   __ __ Hours per day

   __ __ __ Minutes per day

   ☐ Don't Know/Not Sure

   ☐ Refused

   [**Interviewer clarification**: Think only about those physical activities you do for at least 10 minutes at a time.]

   [**Interviewer probe**: An average time for one of the days on which you do vigorous activity is being sought. If the respondent can't answer because the pattern of time spent varies widely from day to day, ask: "How much time in total would you spend **over the last 7 days** doing vigorous physical activities?"

   __ __ Hours per week

__ __ __ Minutes per week

☐ Don't Know/Not Sure

☐ Refused

Think about all the *moderate* activities which take *hard physical effort* that you did in the last 7 days. Vigorous Moderate physical activities make you breathe somewhat harder than normal and may include carrying light loads, bicycling at a regular pace, or doubles tennis. Do not include walking. Again, think about only those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities?

_____ Days per week

☐ Don't Know/Not Sure

☐ Refused

[**Interviewer clarification**: Think only about those physical activities that you do for at least 10 minutes at a time]

[**Interviewer Note**: *If respondent answers zero*, refuses or does not know, skip to Question 18]

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

__ __ Hours per day

__ __ __ Minutes per day

☐ Don't Know/Not Sure

☐ Refused

[**Interviewer clarification**: Think only about those physical activities that you do for at least 10 minutes at a time.]

[**Interviewer probe**: An average time for one of the days on which you do moderate activity is being sought. If the respondent can't answer because the pattern of time spent varies widely from day to day, or includes time spent in multiple jobs, ask: "What is the total amount of time you spent over the **last 7 days** doing moderate physical activities?"

__ __ Hours per week

__ __ __ Minutes per week

☐ Don't Know/Not Sure

☐ Refused

THINK ABOUT THE TIME YOU SPENT WALKING IN THE LAST 7 DAYS. THIS INCLUDES AT WORK AND AT HOME, WALKING TO TRAVEL FROM PLACE TO PLACE, AND ANY OTHER

WALKING THAT YOU MIGHT DO SOLELY FOR RECREATION, SPORT, EXERCISE, OR LEISURE.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?
_____ Days per week

☐ Don't Know/Not Sure
☐ Refused

[**Interviewer clarification**: Think only about the walking that you do for at least 10 minutes at a time.]

[**Interviewer Note**: *If respondent answers zero*, refuses or does not know, skip to Question 20]

6. How much time did you usually spend **walking** on one of those days?
__ __ Hours per day

__ __ __ Minutes per day

☐ Don't Know/Not Sure

☐ Refused

[**Interviewer probe**: An average time for one of the days on which you walk is being sought. If the respondent can't answer because the pattern of time spent varies widely from day to day, ask: "What is the total amount of time you spent walking over **the last 7 days**?"

__ __ Hours per week

__ __ __ Minutes per week

☐ Don't Know/Not Sure

☐ Refused

THINK ABOUT THE TIME YOU SPENT SITTING ON WEEK DAYS DURING THE LAST 7 DAYS. INCLUDE TIME SPENT AT WORK, AT HOME, WHILE DOING COURSE WORK, AND DURING LEISURE TIME. THIS MAY INCLUDE TIME SPENT SITTING AT A DESK, VISITING FRIENDS, READING OR SITTING OR LYING DOWN TO WATCH TELEVISION.

7. During the last 7 days, how much time did you usually spend ***sitting*** on a **week day**?
__ __ Hours per weekday

__ __ __ Minutes per weekday

☐ Don't Know/Not Sure

☐ Refused

[**Interviewer clarification**: Include time spent lying down (awake) as well as sitting]

[**Interviewer probe**: An average time per day spent sitting is being sought. If the respondent can't answer because the pattern of time spent varies widely from day to day, ask: "What is the total amount of time you spent *sitting* last **Wednesday**?"

__ __ Hours on Wednesday

__ __ __ Minutes on Wednesday

☐ Don't Know/Not Sure

☐ Refused

Appendix 3: Western Ontario and McMaster Universities Arthritis Index (WOMAC)

Rate the following today. Place a mark on the line:

Referring to your knee, Do you have (This is not in questionnaire but is implicit)

PAIN none severe

Walking on a flat surface

Going Up and down stairs

At night while in bed

Sitting or lying

Standing upright

STIFFNESS

After first awakening

Later in the day

FUNCTIONAL DEFICIT

Descending stairs

Ascending stairs

Rising from bed

Rising from sitting

Putting on socks

Taking off socks

Bending to the floor

Lying in bed

Walking on flat

Getting in/out of bath

Standing

Sitting

Getting in/out of the car

Getting on/off toilet

Heavy domestic chores

Light domestic chores

Shopping

Appendix 4: Assessment of Quality of Life instrument (AQoL)

Assessment of Quality of Life (AQOL)

INSTRUCTIONS:

Please circle the alternative that best describes you during the last week.

ILLNESS

1. Concerning my use of prescribed medicines:

A. I do not or rarely use any medicines at all.
B. I use one or two medicinal drugs regularly.
C. I need to use three or four medicinal drugs regularly.
D. I use five or more medicinal drugs regularly.

2. To what extent do I rely on medicines or a medical aid? (NOT glasses or a hearing aid.) (For example: walking frame, wheelchair, prosthesis etc.)

A. I do not use any medicines and/or medical aids.
B. I occasionally use medicines and/or medical aids.
C. I regularly use medicines and/or medical aids.
D. I have to constantly take medicines or use a medical aid.

3. Do I need regular medical treatment from a doctor or other health professional?

A. I do not need regular medical treatment.
B. Although I have some regular medical treatment, I am not dependent on this.
C. I am dependent on having regular medical treatment.
D. My life is dependent upon regular medical treatment.

INDEPENDENT LIVING

4. Do I need any help looking after myself?

A. I need no help at all
B. Occasionally I need some help with personal care tasks.
C. I need help with the more difficult personal care tasks.
D. I need daily help with most or all personal care tasks.

5. When doing household tasks: (For example, preparing food, gardening, using the video recorder, radio, telephone or washing the car)

A. I need no help at all.

B. Occasionally I need some help with household tasks.
C. I need help with the more difficult household tasks.
D. I need daily help with most or all household tasks.

6. Thinking about how easily I can get around my home and community:

A. I get around my home and community by myself without any difficulty.
B. I find it difficult to get around my home and community by myself.
C. I cannot get around the community by myself, but I can get around my home with some difficulty.
D. I cannot get around either the community or my home by myself.

SOCIAL RELATIONSHIPS

7. Because of my health, my relationships (for example: with my friends, partner or parents) generally:

A. Are very close and warm.
B. Are sometimes close and warm.
C. Are seldom close and warm.
D. I have no close and warm relationships.

8. Thinking about my relationship with other people:

A. I have plenty of friends, and am never lonely.
B. Although I have friends, I am occasionally lonely.
C. I have some friends, but am often lonely for company.
D. I am socially isolated and feel lonely.

9. Thinking about my health and my relationship with my family:

A. My role in the family is unaffected by my health.
B. There are some parts of my family role I cannot carry out.
C. There are many parts of my family role I cannot carry out.
D. I cannot carry out any part of my family role.

PHYSICAL SENSES

10. Thinking about my vision, including when using my glasses or contact lenses if needed:

A. I see normally.
B. I have some difficulty focusing on things, or I do not see them sharply.
For example: small print, a newspaper, or seeing objects in the distance.
C. I have a lot of difficulty seeing things. My vision is blurred.
For example: I can see just enough to get by with.
D. I only see general shapes, or am blind. For example: I need a guide to move around.

11. Thinking about my hearing, including using my hearing aid if needed:

A. I hear normally.
B. I have some difficulty hearing or I do not hear clearly.
For example: I ask people to speak up, or turn up the TV or radio volume.
C. I have difficulty hearing things clearly. For example: Often I do not understand what is said. I usually do not take part in conversations because I cannot hear what is said.
D. I hear very little indeed. For example: I cannot fully understand loud voices speaking directly to me.

12. When I communicate with others: (For example: by talking, listening, writing or signing)

A. I have no trouble speaking to them or understanding what they are saying.
B. I have some difficulty being understood by people who do not know me. I have no trouble understanding what others are saying to me.
C. I am only understood by people who know me well. I have great trouble understanding what others are saying to me.
D. I cannot adequately communicate with others.

PSYCHOLOGICAL WELLBEING

13. If I think about how I sleep:

A. I am able to sleep without difficulty most of the time.
B. My sleep is interrupted some of the time, but I am usually able to go back to sleep without difficulty.
C. My sleep is interrupted most nights, but I am usually able to go back to sleep without difficulty.
D. I sleep in short bursts only. I am awake most of the night.

14. Thinking about how I generally feel:

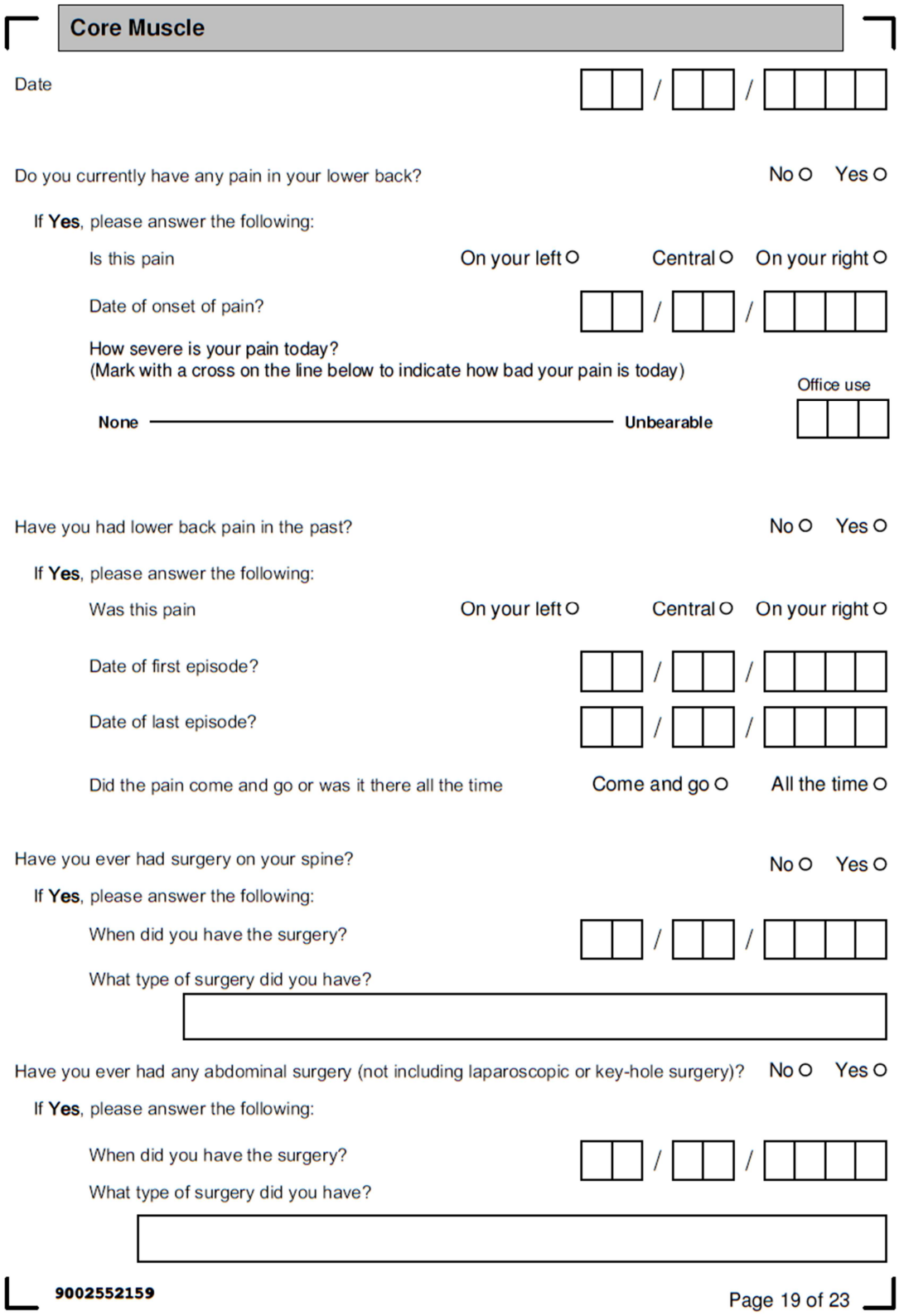
A. I do not feel anxious, worried or depressed.
B. I am slightly anxious, worried or depressed.
C. I feel moderately anxious, worried or depressed.
D. I am extremely anxious, worried or depressed.

15. How much pain or discomfort do I experience?

A. None at all.
B. I have moderate pain.
C. I suffer from severe pain.

D. I suffer unbearable pain.

Appendix 5: Core muscle questionnaire



Core Muscle

Date ☐☐ / ☐☐ / ☐☐☐☐

Do you currently have any pain in your lower back? No ○ Yes ○

If **Yes**, please answer the following:

Is this pain On your left ○ Central ○ On your right ○

Date of onset of pain? ☐☐ / ☐☐ / ☐☐☐☐

How severe is your pain today?
(Mark with a cross on the line below to indicate how bad your pain is today)

Office use ☐☐☐

None ——————————— **Unbearable**

Have you had lower back pain in the past? No ○ Yes ○

If **Yes**, please answer the following:

Was this pain On your left ○ Central ○ On your right ○

Date of first episode? ☐☐ / ☐☐ / ☐☐☐☐

Date of last episode? ☐☐ / ☐☐ / ☐☐☐☐

Did the pain come and go or was it there all the time Come and go ○ All the time ○

Have you ever had surgery on your spine? No ○ Yes ○

If **Yes**, please answer the following:

When did you have the surgery? ☐☐ / ☐☐ / ☐☐☐☐

What type of surgery did you have?

Have you ever had any abdominal surgery (not including laparoscopic or key-hole surgery)? No ○ Yes ○

If **Yes**, please answer the following:

When did you have the surgery? ☐☐ / ☐☐ / ☐☐☐☐

What type of surgery did you have?

9002552159 Page 19 of 23

Core Muscle continued

Females only: How many children have you had? ☐☐

How many children were delivered by caesarean section? ☐☐

In the past 12 months have you had leaking urine?

Never ○
Rarely ○
Sometimes ○
Often ○

RT Ultra Sound

Date taken: ☐☐ / ☐☐ / ☐☐☐☐

Room Temperature ☐☐.☐ °C

Measures taken

Measure	Resting	Contraction	Comments
Multifidus	Yes ○ No ○	Yes ○ No ○	
TrA/IO/EO	Yes ○ No ○	Yes ○ No ○	

Appendix 6: Case Report Form

VIDEO STUDY

Visit 2 (0 Weeks) - RANDOMISATION

Visit Date..... ☐☐/☐☐/☐☐☐☐ DD / MM / YYYY

RANDOMISATION CODE
A randomisation code will be assigned to the participant if the inclusion and exclusion criteria have been met **R** ☐☐☐☐

	ANALGESIC USE	
	YES	NO
Has the subject withheld taking anti-inflammatory and analgesic medications prior to appointment If YES, continue with questionnaires. If NO, allow the subject to complete all BUT the WOMAC Questionnaire. Ask subject to withhold analgesic and inflammatory medications from today and complete the WOMAC questionnaire at home. The questionnaire is then to be returned in pre-addressed, pre-paid envelopes.	☐	☐

Please fill in the medical and medication history:

SURGICAL HISTORY	
Previous Surgical Procedures	Date of Procedure (DD/MM/YYYY)
If the subject is currently taking any medications for any of the above procedures, ensure that details are recorded in the Concomitant Medications record.	

CO-MORBIDITIES				
Have you ever been told by your Dr. or a nurse that you have any of the following conditions?			If yes, do you currently have these conditions?	
	YES	NO	YES	NO
Diabetes	☐	☐	☐	☐
Osteoporosis	☐	☐	☐	☐
High Blood Pressure	☐	☐	☐	☐
Asthma	☐	☐	☐	☐
Bronchitis	☐	☐	☐	☐
Emphysema	☐	☐	☐	☐
Heart Attack	☐	☐	☐	☐
Stroke	☐	☐	☐	☐
Angina	☐	☐	☐	☐
High Cholesterol	☐	☐	☐	☐
None of the above	☐	☐	☐	☐

MEDICAL HISTORY	
CURRENT MEDICAL CONDITIONS	Date of Onset (DD/MM/YYYY)
If the subject is currently taking any medications for any of the above procedures, ensure that details are recorded in the Concomitant Medications record.	

CONCOMITANT MEDICATIONS

Is the subject currently taking **cholesterol lowering agents**? YES ☐ NO ☐

If YES please specify below

Generic Name Brand name	Dosage	Frequency	Route	Start date DD/MM/YYY	Duration (years, months)
atorvastatin Lipitor					
cholestyramine Questran					
colestipol Colestid granules					
ezetimibe Ezetrol, Vytorin					
fenofibrate Lipidil					
fluvastatin Lescol, Vastin					
Nicotinic acid					
gemfibrozil Ausgem, Gemhexal, Jezil, Lipazil					
pravastatin Cholstat, Lipostat, Liprachol, Lopid, Pravachol					

rosuvastatin Crestor					
simvastatin Lipex, Ransim, Simvabell, Simvahexal, Simvar, Zimstat, Zocor					

CONCOMITANT MEDICATIONS					
Is the subject regularly taking **NSAIDS**? YES NO If Yes, provide details below ☐ ☐					
SIMPLE					
Generic name Brand name	Dosage	Frequency	Route	Start date	Duration (years,months)
Diclofenac Diclofenac-BC, Diclohexal, Dinac, Fenac, Genrx Diclofenac, Hexal Diclac, Imflac, Voltaren					
Diflunisal					
Ibruprofen Advil, Brufen, Bugesic, Butalgin, Herron Blue, Iprofen, Nurofen, Nurolasts, Panafen, Profen, Rafen, Tri-Profen					
Indomethacin Arthrexin, Indocid,					
Ketoprofen Orudis, Oruvail,					
Ketorolac Toradol					
Mefenamic Acid Mefic, Ponstan					
Naproxen Aleve, Anaprox, Crysanal, Eazydayz, Femme-Free, Inza, Naprogesic, Naprosyn, Proxen,					

Phenylbutazone					
Piroxicam Feldene, Genrx Piroxicam, Mobilis, Pirohexal-D					
Sulindac Aclin					
Tiaprofenic Acid Surgam					
Tenoxicam					
Celecoxib Celebrex					
Parecoxib Dynastat					
Meloxicam Mefic. Mobic, Movalis					
Lumiracoxib Prexige					
COMBINATION SIMPLE					
Generic name Brand name	Dosage	Frequency	Route	Start date	Duration (years,months)
Diclofenac, Misoprostol Arthrotec					

What is the subject's daily intake of **NSAID**s? □□□ □. □ mg

If dose not taken every day, calculate the average daily dose. □□□ □. □ mg

CONCOMITANT MEDICATION					
Is the subject regularly taking **analgesic medications**? YES □ NO □ If Yes, provide details below					
SIMPLE					
Generic name Brand name	Dosage	Frequency	Route	Start date	Duration (years, months)
Aspirin					

Alka-Seltzer, Aspro Clear, Disprin, Ecotrin, Solprin					
Paracetamol Duatrol SR, Dymadon, Febridol, Panadol, Parahexol, Parmol, Perfalgan					
COMBINATION SIMPLE					
Generic name Brand name	Dosage	Frequency	Route	Start date	Duration (years, months)
Aspirin; Codeine Aspalgin, Codiphen, Codis, Dispirin Forte, Veganin					
Codeine; Paracetamol Codalgin, Codapane, Codral, Dymadon Co, Painstop, Panadeine, Panamax Co					
Codeine, Paracetamol, Doxylamine Succinate Codalgin Plus, Fiorinal, Mersyndol, Panalgesic					
Aspirin; Dihydrocodeine Codox					
NARCOTIC SIMPLE					
Generic name Brand name	Dosage	Frequency	Route	Start date	Duration (years, months)
Fentanyl Actiq					
Morphine Anamorph, Kapanol, MS Contin, MS Mono, Ordine, Sevredol					
Codeine Phosphate Codeine Phosphate, Dolaforte					
Destropropoxyphene Doloxene					
Oxycodone Endone, Oxycontin, Oxynorm, Proladone					
Tramadol Genrx Tramadol, Tramal, Tremedo, Zydol					

Methadone Physeptone					
Buprenorphine Temgesic					
NARCOTIC COMBINATION SIMPLE					
Generic name Brand name	Dosage	Frequency	Route	Start date	Duration (years, months)
Dextropropoxyphene Hydrochloride, paracetamol Capadex, Di-Gesic, Paradex					
Codeine phosphate; paracetamol Codalgin Forte, Codapane Forte, Dymadon Forte, Panadeine Forte, Prodeine,					

CONCOMITANT MEDICATION					
Is the subject regularly taking osteoporosis medications? YES ☐ NO ☐ If Yes, provide details below					
Generic name Brand name	Dosage	Frequency	Route	Start date	Duration (years, months)
alendronate Alendro, Fosamax					
Alendronate + Vitamin D Fosamax Plus					
Calcium Caltrate, Citrocal					
calcitriol Calcijex, Calcitriol, Kosteo, Rocaltrol, Sitriol					
etidronate Didrocal, Didronel					
risedronate Actonel					
Risedronate + calcium Actonel combi					
raloxifene Evista					

Strontium ranelate Protos					
teriparatide Forteo					
Vitamin D ostelin					

CONCOMITANT MEDICATIONS

Is the subject taking low dose aspirin each day (≤150mg/day)? YES ☐ NO ☐

If Yes, provide details below

Aspirin name	Dosage	Frequency	Route	Start date DD/MM/YYYY	Duration (years, months)

CONCOMITANT MEDICATIONS

Does the subject take **any other** medications? (Ask to see ALL medications used)? YES ☐ NO ☐

If Yes, provide details below

Brand Name	Dosage	Frequency	Route	Start date	Duration (years, months)
Glucosamine					
Chondroitin					
Glucosamine + Chondroitin					
Fish oil					
Other					

PHYSICAL EXAMINATION	
Height (without shoes) Stadiometer type Leicester ☐ Other ☐ ..... Stadiometer Number ☐	cms
Weight (without shoes but clothed) Scale type Heine ☐ Other ☐ ..... Scales Number ☐	kgs
Girth measurement: hip Measurement 1 ☐☐☐.☐ cm Measurement 2 ☐☐☐.☐ cm Measurement 3 ☐☐☐.☐ cm	
Girth measurement: waist Measurement 1 ☐☐☐.☐ cm Measurement 2 ☐☐☐.☐ cm Measurement 3 ☐☐☐.☐ cm	
Leg muscle strength	

Measurement 1 ☐☐☐ Kg

Measurement 2 ☐☐☐ Kg

Measurement 3 ☐☐☐ Kg

Hand grip strength

Which is your dominant hand? Right ☐ Left ☐

Left

Measurement 1 ☐☐☐ Kg

Measurement 2 ☐☐☐ Kg

Measurement 3 ☐☐☐ Kg

Right

Measurement 1 ☐☐☐ Kg

Measurement 2 ☐☐☐ Kg

Measurement 3 ☐☐☐ Kg

Upper Arm Blood Pressure

OMRON HEM907 Digital Automatic Blood Pressure Monitor number ☐

Room Temperature ☐☐.☐ degrees celcius

Time participant lying ☐☐:☐☐

Arm circumference ☐☐.☐ cm

Cuff size Small (17-22 cm) ☐

Regular (22-32 cm) ☐

Large (32-42cm) ☐

Arm used R ☐ (Please use right arm) L ☐

If left arm used, please specify why

Right arm injured ☐

Right arm amputated ☐

Recent surgery to right arm ☐

Other (please specify) ☐

Time first reading taken ☐☐:☐☐

Please allow interval of at least 30 seconds between each reading

Measurement 1 ☐☐☐/☐☐☐ mmHg

Measurement 2 ☐☐☐/☐☐☐ mmHg

Central Blood Pressure

Measurement 1 ☐☐☐/☐☐☐ mmHg

Measurement 2 ☐☐☐/☐☐☐ mmHg

Aortic pulse wave velocity

Measurement 1 ☐☐☐.☐ m/s

Measurement 2 ☐☐☐.☐ m/s

Body fat BIA analyser

	YES	NO
Has body fat BIA analyser been performed?	☐	☐

If no state reason a. refusal
b. physical restrictions
c. other…….....

Date taken……
Time taken.....

Right Side ☐ Left Side ☐ Please specify reason.....
(Right side preferred)

	Measurement 1	Measurement 2	Average
Resistance (ohms)	☐☐☐	☐☐☐	☐☐☐
Reactance (ohms)	☐☐☐	☐☐☐	☐☐☐

*Resistance values must be within 1% of each other, otherwise repeat

Fat-free mass (FFM) (kg) ☐☐☐.☐

% Fat-free mass (FFM) ☐☐.☐

Fat mass (kg) ☐☐☐.☐

% Fat mass ☐☐.☐

Body Frame Size:

Height (cm) ☐☐☐.☐

Wrist circumference (cm) ☐☐.☐

Height/wrist circumference ☐☐.☐

Less than 10.4	Small frame	☐
Between 9.6 and 10.4	Medium frame	☐
Less than 9.6	Large frame	☐

Daily Activity Level

The "Daily Activity Level" describes the amount of physical work associated with the individual's typical daily routine. It is important to select an activity level that is appropriate to the amount of activity that the person sees on ***an average daily basis.*** ☐

• Very Light (No Exercise)

Seated and standing activities, painting, driving, laboratory work, typing, sewing, ironing, cooking, playing cards, playing a musical instrument ☐

• Light (Some Exercise)

Walking on a level surface at 2.5 to 3 mph (4 - 4.8 kph), garage work, carpentry, restaurant trades, house-cleaning, child care, golf, sailing, table tennis ☐

• Moderate (Moderate Exercise)

Walking 3.5 to 4 mph (5.6 - 6.5 kph), weeding and hoeing, carrying a load, cycling, skiing, tennis, dancing ☐

• Heavy (Athletic)

Walking with a load uphill, tree felling, heavy manual digging, basketball, climbing, football, soccer ☐

• Exceptional (Elite Athlete)

Extremely strenuous physical activity

VAS PAIN

	YES	NO
Does the subject experience symptomatic knee osteoarthritis for in most days of the last month a) Knee pain [with a pain visual analogue scale (VAS, 0-100 mm) of at least 20 mm]	☐	☐
Actual knee pain score(s) ----------(L)	……..	
Actual knee pain score(s) ----------(R)	……..	

QUESTIONNAIRES				
	Supplied		Completed	
	YES	NO	YES	NO
WOMAC	☐	☐	☐	☐
AQoL	☐	☐	☐	☐
Low back pain questionnaire	☐	☐	☐	☐
Foot pain questionnaire	☐	☐	☐	☐
Diet CCV Barcode ☐☐☐☐	☐	☐	☐	☐
International Physical Activity Questionnaire (IPAQ, short form)	☐	☐	☐	☐
Patient Heath Questionnaire-9 (PHQ-9)	☐	☐	☐	☐

KNEE OSTEOARTHRITIS HISTORY	
With regard to the pain in your **study-selected knee**;	
How long have you experienced pain in that knee?	…….years
Have you had previous surgery to this knee?	☐YES ☐NO
If yes, what type of surgery?	☐Arthroscopy ☐Open Surgery ☐Unknown.....
If yes, when did you have surgery?	Year: ……

Have you had a previous injury to **this** knee, requiring use of walking stick, frame or wheelchair? If so, how many years ago	☐YES ☐NO …….Years

JOINT OSTEOARTHRITIS HISTORY	
Over the past month have you had pain on most days in any of the following joints?	☐ Other knee. **Not** the one being investigated in this study ☐ Lower Back ☐ Neck ☐ Shoulder ☐ Hands ☐ Other (details)……. ☐ No others

EDUCATION	
What is highest level of education?	☐ Didn't finish high school ☐ Finished high school ☐ Trade/Apprenticeship ☐ Certificate/Diploma ☐ Bachelor degree or higher ☐ Didn't answer

EMPLOYMENT HISTORY	
What is your current work status?	☐Full-time employed ☐Part-time/casual employment ☐Unemployed ☐Home Duties ☐Retired

What kind of work have you done for most of your life?	☐ Student ☐ Other Please specify ……..……... ☐ Manual ☐ Office/Professional ☐ Not Applicable

SMOKING	
1. Have you ever been a "regular smoker"? If "NO" go to next section Note: A "regular smoker" is someone who has smoked at least 7 cigarettes, cigars or pipes every week for at least 3 months.	☐ YES ☐ NO Years……Months..……
2. At what age did you first become a "regular smoker"?	……Years of age. ☐ YES ☐ NO
3. Are you currently a "regular smoker"? If no, go to question4 If yes, skip to question 5	……Years of age.
4. How old were you when you last gave up being a "regular smoker"?	……
5. How many cigarettes, pipes, or cigars DO/DID you smoke daily on week days?	…….
6. How many cigarettes, pipes, or cigars DO/DID you smoke daily on weekends?	

SUN EXPOSURE

In summer, during weekends and holidays, how much time would you normally have spent in the sun in last year?	< 1 hr a day……. ☐1 1 to 2 hrs per day….☐2 2 to 3 hrs per day….☐3 3 to 4 hrs per day….☐4 ≥ 4 hrs a day……☐5
In winter, during weekends and holidays, how much time would you normally have spent in the sun in last year?	< 1 hr a day……. ☐1 1 to 2 hrs per day….☐2 2 to 3 hrs per day….☐3 3 to 4 hrs per day….☐4 ≥ 4 hrs a day……☐5
In summer, how much did your activities (playing, day sports, spectator sports, gardening, walking, working activities, etc.) take you outside in the last year?	Not that often……☐1 A moderate amount …☐2 Quite a lot…… ☐3 Virtually all the time. .☐4
In winter, how much did your activities (playing, day sports, spectator sports, gardening, walking, working activities, etc.) take you outside in the last year?	Not that often……. ☐1 A moderate amount …☐2 Quite a lot…….. ☐3 Virtually all the time. .☐4
When outside in summer, how often did you use a sunscreen or make sure you were 'covered up' for the last year?	Never / rarely……☐1 Occasionally…….☐2 Most of the time……☐3 Always / almost always ☐4

BLOOD TESTS		
	YES	NO
Blood samples from the first visit can be used?		

If no, please answer the following: Has a blood sample been taken for 25-(OH) D?	☐	☐
Has a blood sample been taken for Calcium/Magnesium/Phosphate/Urea/Creatinine?	☐	☐
Time samples taken: _____ Signature: _____Date_____		

	MRI	
	YES	NO
Have affected knee MRI been booked? Date taken…… If no state reason a. refusal b. physical restrictions c. claustophobic d. not to have MRI e. other……	☐	☐

	Real Time Ultrasound	
	YES	NO
Has Real Time Abdominal Ultrasound been performed (in Hobart)? Date taken…… If no state reason a. refusal b. physical restrictions c. other……	☐	☐

(INSERT U/S INTERVIEW FORM)

VISIT 2 TEST RESULT SUMMARIES		
		Comments if applicable
25-(OH)D	…….nmol/L	
Calcium	…….mmol/L	
Magnesium	…….mmol/L	
Phosphate	…….mmol/L	

Urea	…….mmol/L	
Creatinine	…….mmol/L	
Other marker		
Other marker		
Other marker		

VISIT 2 TEST RESULT SUMMARIES	
	Comments if Applicable
MRI REPORT	
KNEE X-RAY REPORT	
REAL TIME ULTRASOUND REPORT	
BODY FAT BIA ANALYSER REPORT	

STUDY MEDICATIONS		
	YES	NO
Has the subject taken the assigned Vitamin D or placebo capsule? Randomisation number..... Comments.....	☐	☐
Number of Vitamin D or placebo capsule issued today for the subject to take home: ..... Has the subject been informed to take their monthly capsule and that they will receive a reminder? Has the subject been informed of the storage and administration of the capsules?	☐ ☐	☐ ☐

I agree to comply with taking my monthly placebo or Vitamin D capsule. If for any reason I do not, I will notify the research officer as soon as possible. I will also notify the research officer should I experience any side effects. Signature of participant: ..... Date:	☐ ☐
Signature of research officer: ..... Signature of witness: ..... Date:	

PREPARATION FOR NEXT APPOINTMENT		
	YES	NO
Has an appointment been made for the Subject's visit 3 at month 3?	☐	☐
Has the subject been issued with a pedometer, had its use explained and been asked to use it over a 7 day consecutive period? Please record details in Pedometer Record Pedometer number_____ If pedometer not issued state reason why: Refusal ☐ Physical restrictions ☐ Unable to comprehend instructions ☐ Other- please specify ☐ ..... If Yes, Please answer the following questions:	☐	☐

Pedometer ID:..... Date given..... Signature of participant:.....	

Appendix 7: MEDLINE, CINAHL, EMBASE AND THE COCHRANE LIBRARY Electronic search strategies for muscles of the trunk and assessment modalities

DATABASE	MEDLINE via PUBMED
DATE	(January 1966 – May 2013)
FILTERS	"Middle Aged + Aged: 45+ years", Middle Aged: 45-64 years" and "Aged: 65+ years"
RESTRICTIONS	None
STRATEGY	
#1	"abdominal muscle*" OR "trunk muscle*" OR "rectus abdominis" OR "internal oblique" OR "external oblique" OR "transversus abdominis" OR "multifidus" OR "core stabil*" OR "core strength*"
#2	"electromyography*", "emg", "real time ultrasound imaging", "rtusi", "real time ultrasound", "rtu", "computerised tomography", "ct", "ct scan*", "magnetic resonance imaging", and "mri".
#3	#1 AND #2
DATABASE	CINAHL (1982 – May 2013)
DATE	(1982 – May 2013)
FILTERS	"45-65 years" and "65+ years",

RESTRICTIONS	None
STRATEGY	
#1	"abdominal muscle*" OR "trunk muscle*" OR "rectus abdominis" OR "internal oblique" OR "external oblique" OR "transversus abdominis" OR "multifidus" OR "core stabil*" OR "core strength*"
#2	"electromyography*", "emg", "real time ultrasound imaging", "rtusi", "real time ultrasound", "rtu", "computerised tomography", "ct", "ct scan*", "magnetic resonance imaging", and "mri".
#3	#1 AND #2
DATABASE	EMBASE
DATE	(1982 – 2013)
FILTERS	None
RESTRICTIONS	None
STRATEGY	
#1	"abdominal muscle*" OR "trunk muscle*" OR "rectus abdominis" OR "internal oblique" OR "external oblique" OR "transversus abdominis" OR "multifidus" OR "core stabil*" OR "core strength*"
#2	"electromyography*", "emg", "real time ultrasound imaging", "rtusi", "real time ultrasound", "rtu", "computerised tomography", "ct", "ct scan*", "magnetic resonance imaging", and "mri".

#3	#1 AND #2
DATABASE	THE COCHRANE LIBRARY
DATE	(1982 – 2013)
FILTERS	None
RESTRICTIONS	None
STRATEGY	
#1	“abdominal muscle*” OR “trunk muscle*” OR “rectus abdominis” OR “internal oblique” OR “external oblique” OR “transversus abdominis” OR “multifidus” OR “core stabil*” OR “core strength*”
#2	“electromyography*”, “emg”, “real time ultrasound imaging”, “rtusi”, “real time ultrasound”, “rtu”, “computerised tomography”, “ct”, “ct scan*”, “magnetic resonance imaging”, and “mri”.
#3	#1 AND #2

Appendix 8: Criteria for the assessment of methodological quality – Part A

List of criteria for the assessment of the methodological quality for cohort, cross-sectional and case control studies. Specifications of these criteria are shown in Appendix II.
All items are assessed scoring: + / - / ?/NA

+ positive (design or conduct adequate); - negative (design or conduct inadequate);
? unclear (item insufficiently described); NA (Not Applicable to this study)

Criteria	V/I
STUDY DESIGN	
a) Prospective design was used	V
b) Withdrawals ≤ 20%	V
c) Information on completers versus withdrawals	I
STUDY POPULATION	
d) Selection before disease was known to be present or at uniform point	V
e) Nonbiased selection of participants and with exclusion criteria applied equally to all	V
f) Description of relevant inclusion and exclusion criteria source population	I
g) Sufficient description of baseline characteristics study population	I
h) Participation rate ≥ 80% or participation rate > 50% and <80%, and a clear description of methods of recruitment and information describing how representative those who agree to participate are in comparison to those who do not agree.	V/I
ASSESSMENT OF TRUNK MUSCLES (MF, RA, TRA, IO AND EO)	
i) Trunk Muscles were assessed identically in the studied population according to a standardized protocol.	V
j) Protocol described an appropriate method of muscle measurement.	V
k) Individual muscles measured are specified.	V
(I) WHERE TRUNK MUSCLES WERE THE OUTCOME THEN: (l) to (o) not applicable if trunk muscles are not the outcome factor.	
l) Information on how determinants were measured	V
m) Method used to measure determinants is valid	V/I
n) Determinants were measured in an identical way for the whole studied population.	V
o) Trunk muscles were measured at least two time points (applicable only for longitudinal design)	V/I
(II) WHERE TRUNK MUSCLES WERE THE DETERMINANTS THEN: (p) to (u) not applicable if trunk muscles are not the determinant	
p) Information on how outcomes were measured is given	V/I
q) Assessor blinded to any outcome measure.	V
r) The outcome measure is valid.	V
s) Reliability study on the outcome measure was conducted (reliability)	V
t) The outcome can be used to measure change over time (responsiveness)	
u) The outcome is measured independently of the trunk muscles.	V
ANALYSIS AND DATA PRESENTATION	

v)	Data presentation of most important outcomes	I
w)	Adjusted for most important confounders	V

V = criterion on validity/ precision; I = criterion on informativeness
A study was considered to be of high quality if the methodological quality score was > 60%.

Appendix 9: Criteria for the assessment of methodological quality – Part B

Specified criteria list for the methodological quality assessment (see Supplementary file 3)

CRITERIA

STUDY DESIGN

a) Positive if a prospective design was used. Also positive in case of a historical （ retrospective) cohort when the determinants were measured before the outcome was determined.

'Don't know' if a historical cohort is used, considering determinants at baseline which are not related to the primary research question for which the cohort is created or in case of ambispective design

b) Positive if the total number of withdrawals was ⩽ 20%; not applicable if design was not prospective cohort

c) Positive if at least 2 out of 5 items below were presented for completers and withdrawals:

- Age
- BMI
- Sex
- Health status (healthy, independent, hospitalized or medical condition)
- Presence or absence of low back pain

not applicable if design was not prospective cohort

STUDY POPULATION

d) Positive if the study population was selected before the outcomes of the measurements were known.

Also positive if (sub-) groups were selected at a uniform point in the study.

e) Positive if participants were drawn from the same source population (primary study base) and exclusion criteria are applied equally to all.

f) Positive if relevant inclusion and exclusion criteria were formulated.

g) Positive if trunk muscles and at least 5 of the following 9 items were reported:

- Number of participants
- Age (mean and measure of variance or confidential interval)
- Sex
- Body Mass Index (BMI) (mean and measure of variance)
- Ethnicity
- Place of recruitment
- Sampling frame of source population (e.g. hospital, primary care, general population etc.)
- Health status (healthy, independent, hospitalized or medical condition)
- Presence or absence of low back pain

h) Positive if the participation rate at baseline was at least 80%, or is between 50 and 80%, and a clear description of methods of recruitment and information describing how representative those who agree to participate are in comparison to those who do not agree is given .

ASSESSMENT OF TRUNK MUSCLES (MULTIFIDUS, RA, TRA, IO AND EO)

i) Positive if there is a description of a standardized method of trunk muscle measurement for the entire studied population

j) Positive if trunk muscle activation, thickness or CSA were measured by RTUS, CT, EMG or MRI in accordance with the criteria set in the study.

k) Positive if individual muscles measured are specified.

(I) WHERE TRUNK MUSCLES WERE THE OUTCOME THEN:

(l) to (o) not applicable if trunk muscles are not the outcome factor.

l) Positive if information on how the determinants were measured is given

m) Positive if the method used to measure the determinants is a valid measure

n) Positive if determinants were measured in an identical way for the whole studied population.

o) Positive if determinants were measured at least two time points. Not applicable if not longitudinal design.

(II) WHERE TRUNK MUSCLES WERE THE DETERMINANT THEN:

(p) to (u) not applicable if trunk muscles are not the determinant

p) Positive if information on how outcomes were measured is given

q) Positive if assessor was blind to any outcome measure.

r) Positive if the outcome measure is valid.

s) Positive if the outcome measure is reliable.

t) Positive if the outcome can be used to measure change over time (longitudinal studies only)

u) Positive if the outcome is measured independently of the trunk muscles.

ANALYSIS AND DATA PRESENTATION

v) Positive if frequency or percentage, mean and standard deviation for a group is given or (or β) or RR with CI or P-value of the outcome(s) were reported. For reliability studies; positive if ICC or agreement scores are reported.

w) Positive if there was at least correction for age, sex, back pain and BMI by means of

matching, restriction or adjustment in the analysis. No applicable in purely descriptive studies or reliability/ validity studies.

Morton SM, Bandara DK, Robinson EM, Carr PE. In the 21st Century, what is an acceptable response rate? Aust N Z J. Public Health.2012 ;36(2):106-8.

Appendix 10: Methodology quality assessment

		Study design			Study population					Assessment of trunk ,muscles			Trunk muscles - outcomes				Trunk muscles - determinants						Analysis		Score	Reliability %
Author	**Year**	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**	**o**	**p**	**q**	**r**	**s**	**t**	**u**	**v**	**w**		
Anderson	2012	−	N/A	N/A	+	+	+	+	+	+	+	+	+	+	+	N/A							+	+	13/14	93%
Anderson	2013	−	N/A	N/A	+	+	+	+	+	+	+	+	+	+	+	N/A	+	−	+	+	+	−	+	+	17/20	85%
Briggs	2007	−	N/A	N/A	+	+	+	−	−	+	+	+	+	+	+	N/A							+	−	10/14	71%
Caix	1984	−	N/A	N/A	+	−	−	−	−	+	+	+	−	−	−	N/A							−	−	4/14	29%
Dickstein	2000	−	N/A	N/A	+	+	+	+	−	+	+	+	+	−	+	N/A							+	−	10/14	71%
Dickstein	2004a	−	N/A	N/A	+	+	+	+	−	+	+	+	+	−	+	N/A							+	−	10/14	71%
Dickstein	2004 b	−	N/A	N/A	+	−	+	+	−	+	+	+	+	−	+	N/A							+	−	9/14	64%
Fukumoto	2012	−	N/A	N/A	+	+	+	+	+	+	+	+	+	+	+	N/A							+	−	12/14	86%
Hanada	2008	−	N/A	N/A	+	+	+	+	+	+	+	+	+	−	+	N/A							+	−	11/14	79%
Hanada	2011	−	N/A	N/A	+	−	+	+	−	+	+	+	+	+	+	N/A							+	−	10/14	71%
Hicks	2005	+	+	+	+	+	+	+	+	+	+	+					+	−	−	−	+	+	+	+	16/19	84%
Hwang	2008	−	N/A	N/A	+	−	+	+	−	+	+	+	+	−	+	N/A							+	−	9/14	64%
Ikezoe	2012	−	N/A	N/A	+	−	+	+	−	+	+	+	+	+	+	N/A							+	−	10/14	71%
Kafri	2005	−	N/A	N/A	+	+	+	+	−	+	+	+	+	+	+	N/A							−	−	10/14	71%
Kai	2008	−	N/A	N/A	+	−	+	+	−	+	+	+	+	−	+	N/A							−	−	8/14	57%
Kalichman	2010	−	N/A	N/A	+	−	+	+	+	+	+	+	+	+	+	N/A							+	+	12/14	86%
Kalichman	2011	−	N/A	N/A	+	−	+	+	+	+	+	+	+	+	+	N/A							+	+	12/14	86%

Kang	2007	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N/A							+	−	15/16	94%
Kataoka	2012	−	N/A	N/A	−	−	+	−	−	−	+	+					−	−	−	−	−	−	−	−	3/17	18%
Marcucci	2007	−	N/A	N/A	+	+	+	+	−	+	+	+	+	−	−	N/A							+	−	9/14	64%
McGill	1999	−	N/A	N/A	+	−	+	+	−	+	+	+	+	−	+	N/A							−	−	8/14	57%
Oguri	2004	−	N/A	N/A	+	−	+	+	−	+	+	+	+	+	+	N/A							+	−	10/14	71%
Ota	2012	−	N/A	N/A	+	−	+	+	−	+	+	+	+	+	+	N/A							+	−	10/14	71%
Pereira	2011	−	N/A	N/A	+	−	+	+	−	+	+	+	+	−	+	N/A							+	−	9/14	64%
Shafaq	2012	+	+	+	+	+	+	+	−	+	+	+	+	+	+	N/A							+	−	14/16	88%
Stetts	2009	−	N/A	N/A	+	−	+	+	−	+	+	+	+	+	+	N/A							+	−	10/14	71%
Stokes	2005	−	N/A	N/A	+	−	+	+	−	+	+	+	+	+	+	N/A							+	−	10/14	71%
Takahashi	2007	−	N/A	N/A	+	−	+	+	−	+	+	+	+	−	+	N/A							−	−	8/14	57%

Appendix 11: The assessment of abdominal and multifidus muscles and their role in physical function in older adults: a systematic review

ELSEVIER

Physiotherapy

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Systematic review

The assessment of abdominal and multifidus muscles and their role in physical function in older adults: a systematic review

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Abstract

Background Age-related changes in the trunk (abdominal and lumbar multifidus) muscles and their impact on physical function of older adults are not clearly understood.
Objectives To systematically summarise studies of these trunk muscles in older adults.
Data sources Cochrane Library, Pubmed, EMBASE and CINAHL were searched using terms for abdominal and MF muscles and measurement methods.
Study selection Two reviewers independently assessed studies and included those reporting measurements of abdominal muscles and/or MF by ultrasound, computed tomography, magnetic resonance imaging or electromyography of adults aged ≥50 years.
Data synthesis A best evidence synthesis was performed.
Results Best evidence synthesis revealed limited evidence for detrimental effects of ageing or spinal conditions on trunk muscles, and conflicting evidence for decreased physical activity or stroke having detrimental effects on trunk muscles. Thicknesses of rectus abdominis, internal oblique and external oblique muscles were 36% to 48% smaller for older than younger adults. Muscle quality was poorer among people with moderate-extreme low back pain and predicted physical function outcomes.
Limitations Study heterogeneity precluded meta-analysis.
Conclusion Overall, the evidence base in older people has significant limitations, so the role of physiotherapy interventions aimed at these muscles remains unclear. The results point to areas in which further research could lead to clinically useful outcomes. These include determining the role of the trunk muscles in the physical function of older adults and disease; developing and testing rehabilitation programmes for older people with spinal conditions and lower back pain; and identifying modifiable factors that could mitigate age-related changes.

Keywords: Systematic review; Older adults; Physical function; Trunk muscles; Abdominal muscles; Multifidus muscles

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Introduction

The muscles of the trunk are essential for normal functional activities such as walking and are involved in control of balance and posture [1]. Research on the influence of low back pain (LBP) on these muscles forms the basis of rehabilitation and motor control programmes used by physiotherapists to address alterations in function of these muscles [2]. Research has focused on the abdominal (internal oblique (IO), external oblique (EO), rectus abdominis (RA) and transversus abdominis (TrA)) and lumbar multifidus muscles (MF), but predominantly in younger adults. While physical capacity, skeletal muscle mass and strength [3] deteriorate with age (sarcopenia), the age-related changes of trunk muscles and the impact of such changes are poorly understood. A comprehensive summary of the current literature is critical to guide current clinical practice aimed at reducing age-related losses in physical function and to identify evidence gaps for future research.

Electromyography (EMG), ultrasound imaging (USI), computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used to assess trunk muscle activation, morphology and function. EMG assesses muscle activation patterns which are associated with muscle function [4]. USI, CT and MRI assess muscle morphology, including thickness and cross-sectional area (CSA), which are associated with the amount of force an individual can develop [5]. CT and MRI can also evaluate muscle composition, which include muscle density or muscle attenuation (MA). Muscle attenuation is a radiological characteristic used to quantify macroscopic accumulation of intramuscular fat (muscle quality). The greater this accumulation, the lower the attenuation score in Hounsfield units (HU) [6].

The validity and reliability of trunk muscle measurements using EMG and imaging techniques have been reported for younger populations [7,8], a variety of factors may affect reliability for older adults. The presence of LBP, chronic disease, increases in water content and intramuscular fat accumulation as well as technical issues such as repositioning of the patient for scanning, muscle activation sequences and rate of imaging have the potential to affect reliability of imaging [9]. Concerns regarding the reliability of EMG measures due to problems with task standardisation, 'out-of-plane' movements and normalisation of EMG signals, have also been documented [8]. It is therefore important to determine the validity and reliability of these measures specifically for older adults.

The first aim of this systematic review was to provide a summary of the evidence for changes in function, composition and morphology of the abdominal and MF muscles and the effects of any changes on the physical function of older adults. The second aim was to document the validity and reliability of measurements of abdominal and MF muscles among older adults.

Methods

Literature search

A systematic literature search was conducted on PubMed, CINAHL, EMBASE and The Cochrane library databases as detailed in Supplementary File 2.

Inclusion/exclusion criteria

Studies were included if they:

- were an observational study or randomised controlled trial assessing abdominal or MF muscles;
- had at least 80% of participants ≥50 years old, or data for ≥50 year olds could be extracted from published results;
- used EMG, USI, CT, or MRI to assess abdominal (RA, EO, IO or TrA) or MF muscles;
- reported:
  - validity/reliability or descriptive data for any those muscles, and/or
  - associations of muscle measures with measures of physical function (excluding bodily functions such as micturition, coughing, sneezing and defecation), and/or
  - associations of muscle measures with other factors including but not limited to age, sex, serum vitamin D, medical conditions and medications.

Studies of post-acute abdominal or post-acute back surgery, animals and cadavers were excluded.

Data collection and analysis

Two reviewers (WAC and TMW) independently screened all titles, abstracts and if required full text articles for inclusion, with differences resolved by consensus. Two reviewers (WAC and AW) independently extracted data from included studies, with a third reviewer (TW) available to adjudicate any disagreements but this was not needed. Data extracted were participant characteristics (age, body mass index (BMI), gender, ethnicity) and study characteristics (number of participants, inclusion/exclusion criteria, study design, trunk muscles measured, assessment method, adjustment for confounders and study setting). Information on measures of validity/reliability and results of any associations tested between the muscles of interest and other factors were extracted as outcomes.

Assessment of methodological quality of studies

Methodological quality was assessed independently by two reviewers (WAC and AW) by an established approach for systematic reviews of observational studies on musculoskeletal topics [10] modified as appropriate for our topic. Twenty-three criteria assessed internal validity and informativeness of the studies (Supplementary File 3). Each criterion

was assessed as met (+), not met (−) or unclear (?) based on the descriptions given in Supplementary File 4. Studies with a score >60% were considered to be high quality [10].

Best evidence synthesis

The marked methodological heterogeneity of the included studies precluded meta-analysis so a best evidence synthesis was undertaken. As the first step, studies were grouped according to the condition or population studied, namely healthy older adults and participants with a specific spinal condition (as described in the individual studies, e.g. vertebral fracture or lumbar degenerative kyphosis, and in which LBP was not the primary outcome measure), non-specific low back pain, stroke and other conditions. Studies reporting reliability were also grouped together. Synthesis was performed separately for each of these groups.

The level of evidence was determined using the criteria of Lievense et al. [10]: strong evidence – generally consistent findings in multiple high-quality cohort studies; moderate evidence – general consistent findings in one high quality cohort study and 2 or more high quality case–control studies or in three or more high quality case–control/cross-sectional studies; limited evidence – general consistent findings in a single cohort study, in one or two case–control studies or in multiple case–control/cross-sectional studies; conflicting evidence – <75% of the studies reported consistent findings; no evidence – no studies found. Reliability was categorised as per Shrout [11] (≤0.10 = virtually none, 0.11 to 0.40 = slight, 0.41 to 0.60 = fair, 0.61 to 0.80 = moderate, and 0.81 to 1.0 = substantial).

Results

Of 2176 potential references, 395 were excluded as duplicates, and 1326 were excluded from abstract and title. A further 427 articles were excluded after full text review, leaving 28 included articles (Supplementary Fig. 1) [4,9,12–37].

Characteristics of included studies

Sixteen cross-sectional and 11 case–control studies, and one longitudinal observational study, were included (Table 1). Fourteen studies used EMG to measure trunk muscle motor activity, reflex latencies, muscle fatigue and postural responses. Six used USI to measure muscle thickness and CSA, two used MRI to measure CSA, and six used CT to measure CSA, muscle density and MA. Twelve studies were of healthy adults, five were of participants with spinal conditions, three were of participants with LBP and six were of participants after stroke. There were single studies of people with Parkinson's disease and with hip osteoarthritis. The number of participants ranged from 3 to 1194 (median = 27) and mean ages ranged from 50 to 88 years. Twenty-two studies (79%) were scored as high quality (Supplementary File 5).

Best evidence synthesis

Measures of reliability

There was limited evidence that abdominal or MF muscle CSA, density or attenuation of older adults can be reliably measured with CT. There was limited evidence that MF muscle CSA can be reliably measured with MRI. There was limited evidence that abdominal muscle thickness can be reliably measured with USI. There was no evidence of the reliability of EMG measures, abdominal muscle measurements using MRI, MF measurements using USI or of the test–retest reliability or validity of any modality.

Moderate to substantial intraclass correlation coefficients (ICCs) were reported for CT measurements of abdominal muscle CSA and attenuation and USI measurements of muscle thickness (ICCs ranged from 0.75 to 1.00, Table 2). Reliability of CT measurements of MF muscle density and CSA, and MRI measurements of CSA, was also moderate to substantial (ICC = 0.70 to 0.99). One USI study reported a Pearson correlation of $r = 0.948$ for intra-observer reliability of RA and EO muscle thickness [31], but this is not a recommended reliability measure. One CT study reported a coefficient of variation of <5% for measurements of CSA and MA of the EO, IO and MF muscles at the L4–L5 vertebral levels [36]. Most reliability measures were obtained from stored images of healthy participants [13,26,31,34,36,37], but one study involved participants with spinal conditions [33].

Evidence in healthy adults

There was limited evidence for a detrimental association between age and abdominal or MF muscle morphology (MA, thickness or CSA) in healthy adults, although not all studies were consistent (Table 3). Data for RA, EO and IO were most consistent, with significantly smaller RA (27% to 38%), EO (23% to 47%) and IO (26% to 48%) muscles in healthy independent older women compared to younger controls [23,32] and these muscles being smaller with increasing age [12]. Abdominal muscle MA was also 33% lower in adults ≥75 years compared with younger controls (30 to 50 years) [13]. Associations of age with MF and TrA were less consistent. In most studies age-related differences in muscle thickness or CSA were small or not statistically significant for the TrA (12% to 23%) and MF (12%) muscles [9,23,32] but MF MA was 51% lower in adults ≥75 years compared with younger controls (30 to 50 years) [13] and age was associated with smaller MF CSA in one study [12].

There was conflicting evidence to support an association between age and EMG measures of abdominal muscles. Hwang et al. [22] reported a 45% decrease in reflex latency of the MF muscle of older compared to younger adults when sudden loads were applied to the upper limbs. Hanada et al. [20] found lower muscle activation of abdominal and MF muscles during hip/knee movements by older adults than in

Table 1
Characteristics of participants and studies.

Author Country year	N[a]	Incl./excl. criteria	Age (mean, SD)	BMI	Gender M (%)	Ethnicity	Study design	Muscles measured	Assess method	Confounders adjusted	Study setting	Quality score	Quality (%)
Studies of healthy adults													
[d]Anderson (USA 2012)	100	[b]Incl: Participants from larger Framingham Heart Study families, residents of Greater New England area, men ≥ 35 y.o., women ≥ 40 y.o., weight < 320 pounds Excl: Participants with only 1 parent in the Framingham Heart Study with a father < 55 y.o. or a mother < 65 y.o.	59.4 (14.6) (M) 58.1 (13.3) (F)	NS	51	NS	Cross sectional	RA, EO, IO, MF	CT	Age, sex, height, body mass	Community based, Mas-sachus. area	13/14	93
[d]Anderson (USA 2013)	60	as above	78.6 (2.7) (M) 78.4 (3.3) (F)	28.4 (4.1) (M) 28 (6.1) (F)	50	NS	Cross sectional	RA, EO, IO, MF	CT	Age group, sex	Community based	17/20	85
Caix (France 1984)	3	NS	14 ('up to' 20) 34 (21 to 50) 3 (>50)	NS	69	NS	Cross sectional	RA, EO, IO TrA	EMG	Sex, age, muscle morphol-ogy, PA, PI	NS	4/14	29
Hanada (Canada 2008)	12	Incl: ≥50 years of age. Asymptomatic or LBP > 8 moths Excl: LBP associated with known pathology, spinal fracture or surgery. Previous spinal fracture. MSK, CR, or Neuro conditions, dizziness, pain or recurrent falls.	68.7 (3.5)	27.2 (3.5)	60	NS	Cross sectional	RA, EO, IO, MF	EMG	NS	Dalhousie University	11/14	79

Hwang (Korea 2008)	15	Incl: healthy volunteers ≤ 30 y.o. younger group and ≥60 y.o. for elderly group	26.7 (3.3) Y 63.1 (2.7) O	NS	53	NS	Cross sectional	ES, MF	EMG	NS	NS	9/14	64
Ikezoe (Japan 2012)	41	Excl: Young: Hx of Trunk muscle or bone disease, LBP, spinal surgery. Excl: elderly: Unstable physical condition, Hx of spinal or lower limb surgery, acute Neuro or severe MSK impairment	20 (0.84) Y 85.7 (5.5) IE 87.8 (6.3) CBR	22.1 (2.3) Y 20.5 (3.2) IE 16.6 (2.1) CBR	0	Japanese	Cross sectional	RA, EO, IO, TrA, MF	USI	NS	Nursing home	10/14	71
Kai (Japan 2008)	5	Incl: Old: 68 to 82 years of age. Young: 19 to 31 years of age Excl: Old: Hx of Neuro or MSK disorders. Young: NS	22.6 (4.4) Y 73 (5.7) O	20.6 (2.8) Y 21.1 (2.2) O	100	NS	Cross sectional	IO, MF	EMG	NS	NS	8/14	57
McGill (Canada 1999)	12	Incl: Participants in good physical condition. Excl: Hx of disabling low back injury, recent recurrent pain	69 (3.5)	NS	42	NS	Cross sectional	RA, EO, IO, MF	EMG	NS	NS	8/14	57
Oguri (Japan 2004)	28	Incl: middle-aged long distance runners and untrained individuals.	[c]61.4 (3) High 62.9 (2.7) Inter 61.4 (2.8) Low	21.8 (1.8) High 22.7 (2.4) Inter 23 (1.6) Low	100	Japanese	Cross sectional	RA, EO	USI	Height, length of extremities	NS	10/14	71

Table 1 (*Continued*)

Author Country year	N[a]	Incl./excl. criteria	Age (mean, SD)	BMI	Gender M (%)	Ethnicity	Study design	Muscles measured	Assess method	Confounders adjusted	Study setting	Quality score	Quality (%)
Ota (Japan 2012)	51	Incl: Healthy physically active women Excl: History of trunk or lower extremity surgery or Neuro impairment, paresis of the lower limbs or a severe MSK impairment.	21 (1.1) Y 34.5 (5.8) YA 58 (4.5) MA 70.6 (2.6) YO 79.7 (2.6) OO	NS	0	Japanese	Cross sectional	RA, EO, IO, TrA	USI	Age, height, weight	NS	10/14	71
Stetts (USA 2009)	12	Incl: Healthy ageing adults Excl: LBP, history of abdominal, spinal or lower limb surgery. Respiratory or neurological disorders. Structural scoliosis, urinary incontinence, BMI > 30, pacemaker, Mini Mental State Exam < 24, severe OA.	72 (9.36)	25.9 (2.96)	25	NS	Cross sectional	TrA, IO, EO	USI	NS	NS	10/14	71
Stokes (UK 2005)	46	Excl: Hx of Neuro, neuromuscular, rheumatological or systemic disease. Pregnancy, medication which may affect muscle size, any skin condition or wound in the area to be scanned. Lifetime LBP interfering with ADL's. Lifetime Hx of spinal fractures, lumbar surgery, scoliosis or spondylolisthesis	L4 40.1 (13) Male, 34.2 (12.8) Female L5 39 (13) Male, 31 (11.7) Female	L4 25.8 (3.2) Male 23 (3.1) Female L5 25.7 (2.9) Male, 22.3 (2.2) Female	L4 43 L5 49	NS	Cross Sectional	LM	USI	NS	NS	10/14	71

Studies of participants with spinal conditions													
Briggs (Australia 2007)	25	Incl: osteoporosis Excl: NS	68.4 (6.7) Fracture 64.0 (8.9) No-fracture	26.1 (4) Fracture 24 (3.3) No-fracture	0	NS	Cross Sectional	MF	EMG	NS	NS	10/14	71
[d]Kalichman (USA 2010)	91	[b]Incl: Participants from larger Framingham Heart Study families, residents of Greater New England area, men ≥ 35 y.o., women ≥ 40 y.o., weight < 320 pounds [b]Excl: Participants with only 1 parent in the Framingham Heart Study with a father < 55 y.o. or a mother < 65 y.o.	54.4 (9.3) LBP 52.2 (11.1) NLBP	28.7 (5.5) LBP 27.6 (4.9) NLBP	49 LBP 57 NLBP	NS	Cross sectional	MF	CT	Spinal degen, age, sex, BMI	NS	12/14	86
[d]Kalichman (USA 2011)	91	as above	50 to 59 $n = 55$ $60 + n = 36$	NS	58	NS	Cross sectional	MF	CT	Age, sex, BMI	NS	12/14	86
Kang (Korea 2007)	108	Incl: PT: Patients with Lumbar degenerative kyphosis (LDK) who underwent corrective surgery from 1997 to 2003. Incl: Controls: Mechanical chronic LBP with or without disc protrusion Excl: Controls: LDK, isthmic spondylolisthesis, spinal fracture, tumour, infection, Hx of previous surgery or presence of lumbar scoliosis exceeding 10°	60.19 (5.89) PT 60.15 (6.23) Controls	24.19 (3.10) PT 26.09 (2.9) Controls	0	Korean	Retrospect case control	MF	MRI	Weight, BMI	Hospital	15/16	94

Table 1 (*Continued*)

Author Country year	*N*[a]	Incl./excl. criteria	Age (mean, SD)	BMI	Gender *M* (%)	Ethnicity	Study design	Muscles measured	Assess method	Confounders adjusted	Study setting	Quality score	Quality (%)
Shafaq (Japan 2012)	107	Incl: PT: Surgery for Lumbar spinal stenosis (LSS) with Degenerative lumbar scoliosis (DSL) Incl: Controls: Surgery for LSS without DSL Excl: adolescent idiopathic scoliosis, previous lumbar surgery, pyogenic scoliosis, or vertebral fracture in the lumbar spine.	70.2 (7.3) PT 69.1 (7.1) Controls	NS	23 PT 24 Controls	Japanese	Case control	MF	MRI	NS	Hospital	14/16	86
Studies of participants with low back pain													
Hanada (Canada 2011)	18	Incl: 50 y.o. or older and LBP > 8/12 for LBP group Excl: LBP associated with unknown pathology, radicular syndrome or cauda equina, spinal fracture, surgery or non-specific LBP	61.4 (9.8) CLBP 64.9 (8.8) NLBP	26 (6.6) CLBP 25.6 (2.4) NLBP	44	NS	Cross sectional	RA, IO, MF	EMG	NS	NS	10/14	71
Hicks (USA 2005)	1515	Incl: 70 to 79 y.o. no difficulty walking 1/4 mile, walking up 10 steps or performing ADL's. no cancer or plans to move from area for 3 years	73.72 (2.88) NLBP 73.6 (2.82) LBP	27.32 (4.58) NLBP 28.86 (5.36) LBP	48	44% Black 56% White	Longitud observatio	RA, lateral Abdo and lumbar Paraspinal	CT	Age, sex, height, race, body fat, muscle CSA, PA, disease status, LBP	Community	16/19	84
Takahashi (Japan 2007)	20	Incl: PT: motion induced intermittent LBP (MILBP) Controls: No Hx of LBP or sciatica Excl: NS	75.7 (5.14) MILBP 74.4 (7.9) Controls	NS	0 MILBP 0 Controls	NS	Case control	RA, ES	EMG	NS	Hospital	8/14	57

Studies of participants after stroke

Dickstein (Israel 2000)	26	Incl: PT: Communicative, 'clear-minded' patients with hemiparesis or hemiplegia following a single unilateral stroke Incl: Controls: Healthy controls Excl: Sensory or motor deficiencies unrelated to stroke	74.2 (9.9) PT 67 (9.6) Controls	NS	54 PT 46 Controls	NS	Case control	RA, EO	EMG	NS	Rehabilitation hospital	10/14	71
Dickstein (Israel 2004a)	80	Incl: PT: a-hemiparesis (or plegia) following first unilateral stroke in the territory of the middle cerebral artery, b-sufficiently stable physical health condition to participate in study c-able to sit without support. Incl: Controls: Healthy controls Excl: cognitive or communication deficits Neuro or MSK disorders unrelated to stroke.	72 (9) PT 71 (9) Controls	NS	54 PT 43 Controls	NS	Case control	ES, RA, EO	EMG	NS	Geriatric rehabilita-tion hospital	10/14	71
Dickstein (Israel 2004b)	80	Incl: PT: hemiparetic patients Incl: Controls: Healthy controls	72 (9) PT 71 (9) Controls	NS	54 PT 43 Controls	NS	Case control	RA, EO	EMG	NS	Geriatric rehabilita-tion hospital	9/14	64

Table 1 (*Continued*)

Author Country year	N[a]	Incl./excl. criteria	Age (mean, SD)	BMI	Gender M (%)	Ethnicity	Study design	Muscles measured	Assess method	Confounders adjusted	Study setting	Quality score	Quality (%)
Kafri (Israel 2005)	31	Incl: PT: hemiparesis due to first ischaemic stroke Incl: Controls: community dwelling individuals free of Neuro or MSK disorders that could interfere with side rolling Excl: aphasia, previous Neuro or orthopaedic disorders limiting performance of side rolling.	71.9 (5.8) PT 65.3 (9.1) Controls	NS	65 PT 50 Controls	NS	Case control	EO	EMG	NS	NS	10/14	71
Marcucci (Brazil 2007)	16	Incl: PT: post unilateral stroke Hemiparesis, Ashworth scale spasticity 1 to 4, Bartel index >85, able to ambulate with or without assistance Incl: Controls: individuals matched by sex, age, height and weight, free of Neuro symptoms Excl: neurological syndromes preventing them from participating in the study	58.7 (9.3) PT 59.5 (11.3) Controls	25 PT 24.8 Controls	75 PT 75 Controls	NS	Case control	RA, EO	EMG	NS	NS	9/14	64
Pereira (Brazil 2011)	24	Incl: Unilateral stroke, able to walk alone or with help. MAS score 1 to 3 and able to perform exercises. Incl: Controls: Healthy controls Excl: Neuro or MSK disorders unrelated to stroke, obesity or cognitive deficits	57.5 (8.5) PT 58.7 (9.7) Controls	24.7 (2.7) PT 25.1 (2.4) Controls	58 PT 58 Controls	NS	Case control	RA, EO, ES	EMG	NS	NS	9/14	64

Other studies													
Fukumoto (Japan 2012)	40	Incl: PT: unilateral or bilateral Hip OA Incl: Controls: Healthy women without hip OA Excl: Hx of limb or back surgery, symptoms affecting knees, ankles or back. RA vestibular, central or peripheral nervous system problems. Dementia	56.8 (6.4) PT 57.7 (6.4) Controls	22.1 (3.8) PT 21.6 (2.6) Controls	0 PT 0 Controls	Japanese	Case control	RA, EO, IO, TrA	USI	NS	Kyoto's university hospital	12/14	86
Kataoka (Japan 2012)	16	Incl: PT: Parkinson's disease (PD) with painful abdominal contractions (PAC). Incl: Controls: PD without PAC Excl: multisystem atrophy, another atypical parkisonian syndrome, non-reducible spine flexion and large vessel disease, infarction or tumour on cranial MRI	77 and 80 PT Age-matched controls	21.3 and 22.8 PT 21.3 (2.5) Controls	50	Japanese	Case control	RA	CT	NS	NS	3/17	18

[a] *N*: number of participants ≥ 50 year.
[b] Information obtained from Parikh et al. [45].
[c] Classification refers to level of training and running participants were engaged in prior to the study.
[d] These studies were conducted on the same population.

NS, not stated; RA, rectus abdominis; EO, external oblique; IO, internal oblique; TrA, transversus abdominis; MF, lumbar multifidus; ES, erector spinae; Y, young; O, old; YA, young adult; YO, young old; OO, old old; MA, middle aged; PA, physical activity; PAI, physical activity index; PI, ponderal index; LBP, low back pain; NLBP, CLBP, chronic low back pain; No low back pain; Abdo, abdominal; MSK, musculoskeletal; CR, cardio-respiratory; Neuro, neurological; Hx, history; IE, independent elderly; CBR, chronic bed ridden; PT, patients; ADL, activities of daily living; Inter, intermediate; degen, degeneration; Prospect, prospective; observatio, observational; Longitud, longitudinal; MAS, Modified Ashworth Scale; OA, osteoarthritis.

Table 2
Reliability measures.

Author	Assessment modality	Measurements tested	Reliability coefficients	Reliability type
Anderson (2013)	CT	CSA EO, IO, MF taken at L3	ICC > 0.75	Intra-observer
		CSA EO, IO, MF taken at L3	ICC > 0.75	Inter-observer
Hicks (2005)	CT	Muscle CSA and attenuation at level L4–L5 EO, IO, MF	CV <5%	Not stated
Kalichman (2010)	CT	Density of MF at levels L3–L5	ICC = 0.94 to 0.99	Intra-observer
		Density of MF at levels L3–L5	ICC = 0.70 to 0.97	Inter-observer
Kang (2007)	MRI	CSA MF taken at level L4–L5	ICC = 0.89 to 0.92	Intra-observer
Shafaq (2012)	MRI	CSA MF, spinal level at which image was taken was not specified	ICC = 0.98	Intra-observer
		CSA MF, spinal level at which image was taken was not specified	ICC = 0.97	Inter-observer
Oguri (2004)	USI	Muscle thickness RA taken 3 cm distal to and right of the umbilicus	r = 0.948	Intra-observer
		Muscle thickness EO taken 10 cm on the 'diagonal rear' of iliocostalis	r = 0.948	Intra-observer
Stetts (2009)	USI	Muscle thickness EO, IO, TrA transducer placed in a transverse plane halfway between ASIS and the lower rib cage, along the axillary line	ICC = 0.95 to 1.00	Intra-observer
			ICC = 0.77 to 0.97	Inter-observer
		Muscle thickness EO, IO, TrA transducer placed in a transverse plane halfway between ASIS and the lower rib cage, along the axillary line		

normative data from younger adults. Caix et al. [15] reported much lower abdominal muscle motor activity among older than younger adults during contralateral axial twisting of the trunk. Contrary to those studies, McGill et al. [30] reported higher motor activation of abdominal muscles among older adults during movements of the trunk, and Kai et al. [25] found no differences between activation of the IO and MF muscles of older and young adult controls when moving from a two-leg to a one-leg standing position [25].

There was conflicting evidence for an association between abdominal or MF muscle measures and physical activity (PA). Oguri et al. [31] found no difference in thickness of the rectus abdominis muscle in endurance compared to untrained men. Conversely, in other studies individuals with higher levels of physical activity had better muscle quality [13] and, at the extreme end of inactivity, chronically bedridden female nursing home residents had greater declines in muscle thickness in abdominal (~33%) and MF (~2%) muscles compared with independent residents [23]. No studies in healthy adults investigated associations between trunk muscle measures and any aspect of physical function included in this review (see inclusion criteria).

Participants with spinal conditions

There was limited evidence for an association between spinal conditions and detrimental changes in MF muscle morphology or muscle activation. Nevertheless, some evidence of a detrimental effect was found in every study of both muscle morphology and muscle activation (Table 4). MF muscle activation was delayed in older adults with osteoporotic vertebral fractures [14]. MF muscle CSA was decreased by 36% in older adults with lumbar degeneration [37]. Similarly, Shafaq et al. [33] reported decreases of MF muscle CSA on the concave side of older adult patients with degenerative lumbar scoliosis (10% to 22%) and on the affected side of patients with lumbar spinal stenosis (15% to 20%) with increases in muscle fat infiltrations in both populations. Kalichman et al. [26,27] reported associations of age and moderate to severe facet joint osteoarthritis with low MF density and an association between increased lumbar lordosis and low MF density.

Participants with LBP

There was limited evidence for an association between MF muscle attenuation and LBP, conflicting evidence for an association between alterations in abdominal or MF muscle activation and LBP and limited evidence supporting there being no association between muscle size and LBP (Table 5). Longitudinally, trunk MA but not muscle area was positively associated with physical functional capacity assessed by the Health ABC Physical Performance Battery [36], with a stronger association for people with than without moderate to severe LBP [36]. Results from the two EMG studies were mixed. Bilateral muscle activation was lower in the RA and higher in the MF muscle with some side differences in IO muscle activity during gait, for older adults with non-specific chronic LBP compared with controls without LBP [21]. Takahashi et al. [35] reported no differences in RA muscle fatigue with mechanical loading among older women with 'motion-induced intermittent LBP' compared with controls.

Participants after stroke

There was conflicting evidence for an association between alterations in abdominal muscle activation and stroke. All studies of patients after stroke used EMG and results were inconsistent (Table 6). Comparing the affected to the non-affected side, some studies reported no difference in symmetry index between groups of patients with hemiparesis and healthy controls or side differences for activation of the RA [17,18,24] or EO muscles [16,24]. Others found either decreased [17,18] or increased [4,29] RA and EO muscle

Table 3
Studies of healthy older individuals.

Author	Factors tested	Results	Statistical methods	Summary
Anderson (USA 2012) CT (12)	RA, IO, EO and MF CSA at Levels L2 to L5 and association with age, sex and body mass	Among 36 to 87 year olds, abdominal and MF muscle CSA was negatively associated with sex and age and positively associated with body mass. The regression models explained 52% to 65% of RA, 20% to 64% of EO, 36% to 63% of IO and 22% to 39% of MF CSA variability.	Linear regression	Muscle CSA is smaller for women, older subjects, and those of lesser weight.
Anderson (USA 2013) CT (13)	Muscle attenuation (MA) of abdominal and MF muscles and association with age, sex and PA	At L3 level: MA was lower among adults ≥75 years old (−15.9 (1.07) HU, $P<0.001$) compared with adults 30 to 50 years and lower in women (−6.9 (0.46) HU, $P<0.001$) compared with men. There was a significant association between PA and low MA (effect sizes not reported)	ANOVA, linear regressions, ANCOVA	RA, EO, IO and MF muscle attenuation was lower among older adults, women and people with decreased physical activity.
Caix (France 1984) EMG (15)	Abdominal muscle motor performance according to age, sex, mass and physical activity	Compared with the younger group ('up to 20' y.o.), the older group (>50 y.o.) showed decreased motor activity of RA in tonus (19%), posture (66%) and movement (98%). The flat abdominals showed decreased motor activity in tonus (64%), posture (80%) and movement (97%).	Not stated	Abdominal muscle activation was lower for participants 50 years or older.
Hanada (Canada 2008) EMG (20)	Abdominal and MF muscle response to change in load	During hip/knee flexion/extension exercises, abdominal muscles activation amplitudes varied according to level (1 to 3) of difficulty (15% to 34% of max voluntary isometric contraction (MVIC)). Muscle activation amplitudes of MF was <10% MVIC and there were little changes between levels of difficulty (7 (3)% to 7 (3)% MVIC)	None	Among healthy adults (65 to 80 years), abdominal muscle activation amplitudes were low to moderate, depending on the level of exercise difficulty. There is low MF muscle activation irrespective of level of exercise difficulty.
Hwang (Korea 2008) EMG (22)	Reflex latencies, flexion movement and flexion moment of the trunk and association with age and upper limb loading	During UL sudden loads: significant age-related delay of multifidus reflex latency during expected loads (mean = −26.08, 95% CI −42.45 to −9.71 ms, $P=0.0026$).	ANOVA	Age-related delay in multifidus muscle reflex activation and trunk flexion movement in response to sudden loading.
Ikezoe (Japan 2012) USI (23)	Abdominal and MF muscles of elderly women and association with age and inactivity	A significant decrease in muscle thickness of RA (36%, 51%), EO (40%, 66%) and IO (48%, 57%) in independent and chronic bedridden elderly women respectively, was found compared with the young women group. A significant decrease in muscle thickness of TrA (52%), MF (30%) was found only in chronically bedridden elderly women compared with the young women group.	ANOVA and Mann–Whitney *U*-tests	Age-related muscle atrophy was smallest for the deep trunk muscles (TrA and MF) of elderly women. Chronically bedridden elderly women had greater decrease in all trunk muscle thickness compared with independent elderly.
Kai (Japan 2008) EMG (25)	Muscular activity of left IO and MF while moving from two-leg standing to one-leg standing in healthy elderly ($n=5$) compared with young ($n=8$) subjects	Higher levels of muscle activity were observed in IO and MF in the young person group, compared with the healthy elderly group. However, the differences were not statistically significant in this small sample. No effect sizes were reported.	Mann–Whitney *U*-test	No significant difference in IO or multifidus muscle activation between young and older adults during the two-leg standing to one-leg standing task.

Table 3 (*Continued*)

Author	Factors tested	Results	Statistical methods	Summary
McGill (Canada 1999) EMG (30)	RA, EO and IO muscle activation and association with age and trunk movement	RA, EO and IO muscle activity was greater in the elderly group compared with a young control group during the flexion ($P=0.0001$) and lateral bending ($P=0.0001$) tasks, but not the axial twisting ($P>0.05$) task. No effect sizes were reported.	Unclear	Greater abdominal muscle activation during trunk flexion and lateral bending tasks among elderly subjects, compared with younger subjects.
Oguri (Japan 2004) USI (31)	RA and EO muscle thickness and association with running training levels	RA muscle thickness was not significantly correlated ($r=0.326$) with weekly training distance. No significant difference was found between mean RA muscle thickness of high level (7.09 mm), intermediate (6.3 mm) or untrained groups (6.3 mm). EO muscle thickness results were not reported.	ANOVA, Tukey's post hoc test, Pearson correlation.	There was no significant difference in RA muscle thickness among older men despite differences in running training levels.
Ota (Japan 2012) USI (32)	RA, EO, IO and TrA muscle thickness and association with age	Muscle thickness (mm) was significantly smaller in older subjects for RA (27 (16)% to 38 (20)% $P<0.01$), EO (23 (13)% to 46 (17)% $P<0.05$)) and IO (26 (17)% to 47 (18)% $P<0.05$)), compared with young controls. There was no significant age effect on TrA (19 (17)% to 23 (25)% $P>0.05$)	ANCOVA, ANOVA, Tukey's post hoc test	Age-related decrease in RA, IO and EO muscle thickness. Non-significant decrease in TrA muscle thickness.
Stokes (UK 2005) USI (9)	CSA and shape of multifidus and association with age	Significant difference in MF shape ratio (AP/Lat) at L5 between the 20 to 29 y.o. (0.89 (0.11)) and the 50 to 69 y.o. (1.12 (0.14)) male groups ($P=0.0001$). No significant age-related change in CSA of MF and no significant differences of MF symmetry between age groups. However, specific data from the 50 to 69 age group was not provided.	*t*-test	Significant difference in shape of multifidus between young and older adults. No significant difference in MF CSA or symmetry at L4 and L5 levels.

RA, Rectus abdominis; EO, External oblique; IO, internal oblique; TrA, Transversus abdominis; MF, Lumbar multifidus, y.o., years old; MF, Lumbar multifidus; CSA, Cross sectional area; MA, Muscle attenuation; PA, physical activity; HU, Hounsfield units; CI, confidence intervals, AP, Antero-posterior; Lat, lateral dimension; mm, Millimetres.

activity on the affected side, during movements of the trunk or hip joint.

Other studies

Only single studies examined associations between abdominal muscle thickness and hip osteoarthritis and painful abdominal contractions among patients with Parkinson's disease (Table 5). Patients with hip osteoarthritis had 3% to 6% thinner abdominal muscles compared with healthy controls [19]. Kataoka et al. [28] reported greater RA thickness for two patients with Parkinson's disease affected by painful abdominal contractions, compared with controls without painful contractions.

Discussion

This systematic review provides a comprehensive assessment of the current literature investigating trunk muscles in older people. Overall, the evidence base has significant limitations, but the available data highlight four key points. Firstly, measurement of stored images of abdominal and MF muscles of older adults can be performed with moderate to substantial reliability using various imaging modalities. Secondly, ageing and possibly decreased physical activity appear to have detrimental effects on the morphology of abdominal and MF muscles. Thirdly, a variety of spinal conditions adversely affect the activation and morphology of MF but LBP appears to mainly affect MA, which in turn affects physical function. Lastly, the effects of stroke on the abdominal and MF muscles and implications for physical function and rehabilitation have not been established.

Consistent evidence was found that measurement of CT, MRI or USI images of older adults' abdominal and MF muscles can be performed with moderate to substantial reliability. Studies of USI test–retest reliability were lacking during the timeframe of our search, but subsequent studies have reported 'good-to-excellent' test–retest reliability for muscle thickness at L4–L5 of older adults with and without LBP [38,39]. Thus, overall, current data are consistent with

Table 4
Studies of participants with spinal conditions.

Author	Factors tested	Results	Statistical methods	Summary
Briggs (Australia 2007) EMG (14)	Associations between vertebral fracture and paraspinal muscle recruitment of subjects with osteoporosis	The time to initiate postural response differed between the non-fracture (epoch 4 = 50 to 25 milliseconds before deltoid onset) and fracture (epoch 5 = 25 to 0 milliseconds before deltoid onset) groups.	*t*-tests, Mann–Whitney *U*-test, ANOVA, Sharpened Bonferroni post hoc test	Paravertebral muscle activation is delayed among older adults with osteoporotic vertebral fractures
Kalichman (USA 2010) CT (26)	Associations between different lumbar spine degenerative features and density of the MF muscle	Density of MF decreases with age ($P < 0.0001$) in people with spinal degeneration features (50 to 59 y.o. 33% of subjects and >60 y.o. 69% of subjects). Moderate to severe facet joint OA was associated with decreased density of multifidus (odds ratio 3.68, CI 1.36 to 9.977).	Chi-square test, *t*-test, Cochrane-Armitage trend test, logistic regression	Significant association between LBP and presence of facet joint OA and decreased density of multifidus
Kalichman (USA 2011) CT (27)	Associations of CT-evaluated lumbar lordosis and density of multifidus	After adjusting for age, sex and BMI, lumbar lordosis angle was positively associated ($P < 0.05$) with density of multifidus (odd ratio 1.06, 95% CI 1.01 to 1.11).	*t*-test, linear regression, logistic regression	Lumbar lordosis angle positively associated with density of multifidus
Kang (Korea 2007) MRI (37)	Paraspinal muscle wasting of lumbar degenerative kyphosis (LDK) patients compared with chronic low back pain (CLBP) patients	MF muscle CSA was smaller (36%, $P < 0.0001$) in the LDK group compared with the CLBP group.	ANOVA, logistic regression, Chi-square test	Older adults with lumbar degenerative kyphosis had significantly smaller MF muscle CSA, compared with CLBP patients
Shafaq (Japan 2012) MRI (33)	Muscle degeneration of patients with lumbar spinal stenosis (LSS) with and without degenerative lumbar scoliosis (DLS)	In the DLS group CSA of MF was smaller on the concave side L3–L5 (CI 51.79, 59.21 $P = 0.035$), L4–L5 (CI 60.52, 70.48 $P = 0.008$) and L5-S1 (CI 72.70, 82.10 $P = 0.0001$). In the LSS group with unilateral radiculopathy CSA of MF was smaller on symptomatic side L4–L5 (CI 61.37, 70.02 $P = 0.007$) and L5-S1 (CI 75.40, 84.00 $P = 0.001$). Increases in fat infiltrations in both populations ranging from 2% to 28% in the lower spinal levels.	Mann–Whitney test, Chi-square test, paired t-test, Pearson correlation	Smaller MF CSA on concave side of DLS patients and on the affected side of LSS patients with unilateral radiculopathy increases in fat infiltrations in both populations at all spinal levels

MF, Lumbar Multifidus; epoch, "The time to initiate a postural response in which EMG amplitude increases above baseline"; OA, osteoarthritis; LBP, low back pain; CSA, cross-sectional area.

previous reports of reliability of measurements of younger adults, especially for USI [7], and support the use of these modalities in both research and clinical settings. Conversely, until the reliability of EMG in older adults is assessed, this modality is of unknown utility.

The differences in thickness of abdominal muscles in older compared to younger adults reported in this review (36% to 48% between 20 and 86 years and 38% to 47% between 21 and 80 years, excluding TrA in both cases) [23,32] are consistent with previously reported estimates of decreases in upper and lower limb muscle CSA with age of 1% per year after age 50 years and in muscle mass of 30% between the ages of 20 and 80 years [40]. The absence of age-related differences in TrA and MF muscles [9,23,32] may be due to their tonic activation and spinal stabilising role, which require them to be active at low levels when in upright positions to counteract the effects of gravity and postural changes during most activities of daily living [41]. In contrast, the more superficial muscles, which have a greater role in torque generation may be influenced by lifestyle factors or clinical and sub-clinical disease. Strategies to maintain trunk muscles may need to be tailored to different muscles.

The potential influence of physical activity on abdominal and MF muscles has been demonstrated in the extreme case of chronically bedridden nursing home residents [23], studies of healthier older adults [13] and in studies of subjects during prolonged bed rest [42] but not in the thickness of RA in endurance vs untrained men [31]. The latter were a small group of relatively active older men (for example undertaking hill walking and golf) which could explain this lack of difference. Overall, the results suggest that physical activity plays an important role in maintaining the size and quality of the abdominal and MF muscle of older adults. These findings have clinical significance because physical activity decreases with ageing and older adults are more likely to undergo periods of bed rest due to injury or illness

Table 5
Studies of participants with low back pain and other studies.

Author	Factors tested	Results	Statistical methods	Summary
Hanada (Canada 2011) EMG (21)	RA, IO and MF muscle activation amplitudes during gait and association with low back pain	Compared with the control group, the LBP group: had lower muscle activation levels of their RA on the right (4% MVIC, $P<0.001$) and left (7% MVIC, $P<0.001$) sides, MF muscle activation was greater on the right (10% MVIC) and left (5% MVIC). Significant activation differences were observed in right IO depending on the phase of gait they were measured and left IO muscle activation levels were not significantly different.	*t*-test, ANOVA, Tukey's post test	Depending on the phase of gait, there were altered RA, IO and multifidus muscle activation levels of older adults with low back pain (LBP) during gait
Hicks (USA 2005) CT (36)	Longitudinal associations between trunk muscle composition, back pain (LBP) and physical function	Trunk muscles MA lower but muscle area was similar in those with compared to without severe LBP. Abdominal and paraspinal muscle attenuation was a significant predictor of composite functional scores ($\beta=0.006$, $P<0.01$). Significant interaction between trunk muscle attenuation but not muscle area and back pain status in predicting physical function for no/mild pain group ($\beta=0.005$, $P=0.043$) and moderate/extreme pain ($\beta=0.011$, $P=0.011$)	Linear regression, *t*-tests	Positive longitudinal association between abdominal and paraspinal muscle attenuation, back pain status and physical function among older adults with low back pain. No interaction between trunk muscle CSA and back pain status.
Takahashi (Japan 2007) EMG (35)	Effect of mechanical load on RA muscle fatigue	RA muscle fatigue was not induced in either controls (−5.3 (12.3) MPF (%/min), 95% CI −14.09 to 3.49) or low back pain group (−1.5 (15.0) MPF (%/min) between 30 and 60 seconds after loading, 95% CI −12.23 to 9.23). (CI values are for the difference of absolute values between groups)	ANOVA, Mann–Whitney *U*-test	No significant changes in RA muscle fatigue with loading in older participants with LBP or those without LBP
Other studies				
Fukumoto (Japan 2012) USI (19)	Abdominal muscle thickness and association with hip osteoarthritis	Compared with healthy controls, abdominal muscles in the OA group were: RA 6%, IO 5% and TrA 3% thinner. However, EO was thicker by 12%. These differences were of no statistical significance in this small sample group.	Mann–Whitney *U*-test	No significant difference in abdominal muscle thickness, except for EO, between individuals with hip OA and healthy individuals
Kataoka (Japan 2012) CT (28)	Activation and muscle thickness in Parkinson's patients with painful abdominal contractions (PAC)	Constant hypertonic activity and greater muscle thickness (mm) of RA (48% L4 and 49% L5 vertebral level) in the 2 patients with PAC compared with 14 controls.	Not stated	Constant hypertonic activity was demonstrated in the rectus abdominis muscle of Parkinson's subjects with painful abdominal contraction

MF, Lumbar Multifidus; epoch, "The time to initiate a postural response in which EMG amplitude increases above baseline"; OA, osteoarthritis; LBP, low back pain; CSA, cross-sectional area.

[43]. Future research investigating the effects of maintaining physical activity in older adults and rehabilitation of trunk muscles after prolonged bed rest is needed. There is also a significant evidence gap on the role of trunk muscles in maintaining long-term physical functioning of older adults.

There was limited, but consistent evidence for an adverse effect of various spinal conditions on activation, attenuation and CSA of the MF muscle [14,26,27,33,37]. Clinically, this suggests that motor control and other rehabilitation programmes used by physiotherapists to target MF muscles may also be useful for older adults affected by spinal conditions. It is less clear if this is also the case for non-specific LBP, though longitudinal data [36] do suggest deterioration in the quality of the MF muscle in the presence of LBP. Furthermore, there was a significant longitudinal association between abdominal and paraspinal MA and greater physical function deficits, with stronger associations seen for participants with moderate-extreme LBP, but with no associations with muscle size. It may be that muscle quality rather than quantity is important functionally in older adults. Although strength and endurance exercise programmes specifically targeting trunk muscles have been devised [2,44], their effectiveness for reducing intramuscular fat accumulation and improving muscle quality is not established. Future studies investigating this could lead to improved exercise programmes for improving physical capacity of older adults, especially those with LBP.

Table 6
Studies of participants after stroke.

Author	Factors tested	Results	Statistical methods	Summary
Dickstein (Israel 2000) EMG (16)	Bilateral activity of RA and EO muscles during basic symmetrical movements and association with hemiparesis	No significant difference in muscle activation of RA (0.85 (0.1) to 0.81 (0.2), $P>0.05$) or EO (0.71 (0.1) to 0.64 (0.2), $P>0.05$) between healthy and hemiparetic subjects. No significant difference in muscle activation RA (0.66 (0.15) to 0.63 (0.21, $P>0.05$) or EO (0.71 (0.13) to 0.59 (0.28), $P>0.05$) between the paretic and non-paretic sides	ANOVA, *t*-test	No differences in RA or EO muscle activation of hemiparetic subjects compared with healthy individuals
Dickstein (Israel 2004a) EMG (17)	Function of RA and EO in voluntary trunk movements and association with stroke	Lower RA and EO muscle activation latency in patients compared with controls ($F(1,69)=3.96$, $P<0.05$). In the patient group, SI of the RA muscle was significantly lower −17 (30)% (concentric), −15 (35)% (eccentric) compared with the control group 2 (22)%, −1 (22)%. SI of EO between patients and controls was not significant.	ANOVA, *t*-test	Impairment of rectus abdominis muscle function on paretic side and also EO to a lesser degree
Dickstein (Israel 2004b) EMG (18)	RA and EO muscle activation and association with hemiparesis	No significant differences in RA anticipatory muscle activation between hemiparetic and control subjects or between sides on hemiparetic subjects. Reduced EO muscle activation on the hemiparetic side ($F(1,74)=4.6$, $P<0.04$). Significant difference in symmetry activation of EO on the paretic side of patients compared with corresponding side of controls ($t(74)=4.84$, $P<0.0001$). No significant difference in RA SI between groups.	ANOVA, linear regression	No difference in anticipatory muscle activation for RA. Reduced EO muscle activation on hemiparetic side
Kafri (Israel 2005) EMG (24)	EO muscle activation during side rolling from supine lying position and association with hemiparesis	In hemiparetic subjects, symmetry index of EO muscle activation on the paretic side, was comparable or lower −0.22 (0.22) than the non-paretic side 0 (0.24), but not significantly different	Paired *t*-test	Among post stroke patients, EO muscle activation symmetry was comparable between paretic and non-paretic sides when rolling from supine to side lying
Marcucci (Brazil 2007) EMG (29)	RA and EO muscle behaviour and association with hemiparesis	During MVIC there were no statistically significant differences in the muscle activation of RA or EO between the paretic RA (73.97 (27.65) μV, EO (69.9 (13.0) μV and control RA (52.44 (6.16) μV, $P=0.46$), EO (97.46 (25.7) μV, $P=0.36$) groups. However, during the hip flexion task the muscle activation level of RA in the hemiparetic group was higher ($P=0.031$) than the control group (hemiparetic group (59 (31)% of MVIC), control group (32 (11)% of MVIC)	Shapiro–Wilk, *t*-test, MANOVA Tukey's post hoc test	Hemiparetic subjects showed increased RA and muscle activity during hip flexion task
Pereira (Brazil 2011) EMG (4)	RA and EO muscle activation and association with hemiparesis	RA muscle activation was higher on the paretic side during leg elevation ($P=0.035$, Cohen's $d=0.94$), during lower trunk rotation ($P=0.017$, $d=0.85$) and during non-paretic side trunk rotation ($P=0.005$, $d=1.22$). EO muscle activation was higher on the non-paretic side during trunk flexion ($P=0.019$, $d=0.75$).	*t*-test, Mann–Whitney test, Shapiro–Wilk test, Wilcoxon test, MANOVA, Box *M* test, *f* test, Tukey's post hoc test	Hemiparetic subjects showed increased RA muscle activity during leg elevation, lower trunk rotation and contralateral trunk rotation. EO activation was higher on non-paretic side during trunk flexion

RA, Rectus abdominis; EO, External oblique; SI, symmetry index.

Reports of abdominal muscle activation from studies of patients after stroke were conflicting. This may be due to the diversity of EMG measures used, the diversity of clinical presentations associated with stroke and movements tested. As we report, reliability of EMG measures in the elderly has not been reported and if low could also contribute to the conflicts between studies. It is possible that addressing trunk muscle function may have clinical relevance for rehabilitation but substantial further research is required. In particular, the lack of investigation of the effects of stroke on abdominal and MF muscle size and quality is an evidence gap that requires further research if we are to understand what role, if any, these muscles have in stroke rehabilitation.

Limitations

We were unable to undertake meta-analysis because the studies were too heterogeneous to pool. However, we performed a systematic review with a best evidence synthesis to maximise the robustness. Not all studies clearly separated age groups when reporting [9], so there has been some minor mixing of data for adults younger than 50 years. Many studies were small (64% had ≤40 participants) and only one was a longitudinal study, which limits the strength of evidence for the review findings. The review was limited to muscle outcome measures assessed with EMG or imaging and does not address the full spectrum of procedures in which muscle structure and function can be assessed.

Conclusion

Overall, the evidence examining EMG and imaging measures of trunk muscles in older people has significant limitations, and the role of physiotherapy interventions aimed at these muscles remains unclear. The results suggest areas in which further research could lead to clinically useful outcomes. These include determining the role of the trunk muscles in the physical function of healthy older adults and in those with disease, in particular stroke; developing and testing rehabilitation programmes for older people with spinal conditions and LBP; identifying modifiable factors that could mitigate age-related changes, including physical activity and testing whether exercise programmes can reduce intramuscular fat accumulation in trunk muscle of older adults.

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Conflict of interest: None declared.

Author contributions: Study conception and design: JAH, GJ, TMW. Acquisition of data: WAC, AW, TMW. Design of data analysis plan: WAC, CLB, TMW. Analysis and interpretation of data: WAC, AW, JAH, CLB, MLC, PO, TMW. Drafting and revisions of manuscript: WAC, AW, JAH, CLB, MMC, PO, GJ, TMW. All authors approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.physio.2016.06.001.

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Appendix 12: Test-retest reliability of measurements of abdominal and multifidus muscles using ultrasound imaging in adults aged 50-79 years

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Technical and measurement report

Test-retest reliability of measurements of abdominal and multifidus muscles using ultrasound imaging in adults aged 50–79 years

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ABSTRACT

Test-retest reliability of the combined process of ultrasound imaging (USI) and image measurement of thickness of abdominal and upper lumbar multifidus (MF) muscles and MF cross sectional area (CSA) of older adults has not been established. Imaging muscles of older adults can be challenging due to age-related changes in the spine and skeletal muscle so establishing test-retest reliability in this population is important. This study aimed to evaluate test-retest reliability of USI of abdominal and MF muscle thickness and MF CSA for adults aged 50–79 years. One operator took single sets of ultrasound images of abdominal and MF muscles of 23 adults aged 50–79 years participating in a clinical trial of vitamin D supplementation for knee osteoarthritis, on two occasions, one week apart. Images were subsequently measured by a single examiner. Test-retest reliability for abdominal muscle thickness and MF CSA was substantial (intraclass correlation coefficients (ICC) > 0.81) and for MF thickness ranged from fair to substantial (ICC 0.55–0.86). The standard error of measurement (SEM) was low (0.02–0.21) in every case. ICCs were low and SEM values were high for percentage thickness change. The substantial test-retest reliability of abdominal and MF (L4-L5) muscle thickness and of MF CSA supports the use of USI as a clinical and research tool to assess abdominal and MF muscle thickness and MF CSA of older adults.

1. Introduction

The muscles of the lumbopelvic region have a role in stability and function of the spine, locomotion and maintenance of posture and balance (Bergmark, 1989; Granacher et al., 2013). However, research on abdominal and lumbar multifidus (MF) muscles in older adults is limited (Cuellar et al., 2016).

Ultrasound imaging (USI) is used clinically and in research to assess muscle morphology. Its reliability in older adults is not yet fully ascertained. There are two key aspects of reliability, namely reliability of repeatedly measuring the same image and test-retest reliability, where the entire imaging process is repeated by the same person days or weeks apart and measurements made on the resulting sets of images (Rousson et al., 2002). Test-retest reliability is critical to clinical practice and longitudinal research where imaging is repeated to monitor patients' progress. This has greater potential for measurement error than just remeasuring the same image due to additional sources of variation, for example, from repositioning the participant and transducer and identification of landmarks (Hides et al., 2007).

The inter and intra-rater reliability of repeatedly measuring ultrasound images of abdominal and multifidus muscles has recently been reported as substantial in adults aged 65–89 years (Wilson et al., 2016), consistent with that in lateral abdominals in adults of mean age 72 years (Stetts et al., 2009). However, despite the critical importance of test-retest reliability to clinical and research practice, in older adults this has only been reported for MF thickness at the L4-L5 spinal level (Sions et al., 2014a,b) (Cuellar

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et al., 2016) and not for MF cross-sectional area (CSA) or abdominal muscle thickness. Test-retest reliability of MF thickness beyond L4-5 is important as MF morphology varies by spinal level (Hides et al., 1995) and clinical conditions such as low back pain (LBP) affect MF at levels additional to L4-5. Therefore, this study aimed to evaluate the test-retest reliability of USI for assessing abdominal and MF muscle thickness and MF CSA at the L2–L5 vertebral levels.

2. Methods

2.1. Participants

Participants were drawn from an USI sub-study on trunk muscles (n = 186) of the "Vitamin D Effect on Knee Osteoarthritis" (VIDEO) clinical trial in Tasmania (n = 261) (Jin et al., 2016). In brief, VIDEO participants aged 50–79 years, with symptomatic knee osteoarthritis for at least six months, and serum 25-(OH)D levels between 12.5 and 60 nmol/L, were recruited from the community. Twenty-three participants from the USI sub-study took part in the reliability study. The USI sub-study was approved by The Tasmania Health and Human Ethics Committee. All participants gave written informed consent. We measured each participant's height by stadiometer, weight by calibrated scales, calculated body mass index (BMI) (weight (kg)/height (m^2)) and ascertained LBP status by questionnaire asking "Do you currently have any pain in your lower back?".

2.2. Image capture and measurement

USI was performed twice, one week apart, using a Phillips HDI 5000 diagnostic ultrasound (Bothwell, WA, USA) in brightness (B) mode, with a hand held 4–7 MHz curved array transducer. All USI was conducted by a physiotherapist who undertook 36 h of practical training in USI from JAH. Single sets of images were obtained to reduce time to accommodate the USI sub-study within the clinical trial.

Transverse images of transversus abdominis (TrA), internal oblique (IO) and external oblique (EO) were obtained at rest and contracted with participants directed to "take a relaxed breath in and out, hold your breath out, and then draw in your lower abdomen without moving your spine" (Hides et al., 2007). Images were obtained along a line halfway between the lower angle of the rib cage and the iliac crest for right, then left, sides. The transducer was oriented transversely such that full vision of all muscle bellies was possible and the fascial insertion of TrA was close to the medial edge of the image with the muscle relaxed. In younger adults, the medial fascial insertion of TrA would be positioned 2 cm from the medial edge of the screen image (Hides et al., 2007), but this was not possible in these older adults due to body habitus. Transverse images of rectus abdominis (RA) were obtained at rest, for right, then left sides, with the transducer oriented transversely and placed lateral to the umbilicus until RA was centred on the screen (Rankin et al., 2006).

For MF thickness, parasagittal images were obtained on the right side at rest and on isometric contraction at L2-L3 to L5-S1 vertebral levels. For the latter, participants were instructed to take a relaxed breath in and out, hold their breath out and try to slowly "swell" and contract the muscle without moving the spine (Hides et al., 2008b). Participants lay prone with one pillow under the abdomen to reduce lumbar lordosis. L2 to L5 spinous processes were palpated, marked with a pen and then confirmed using USI (Wallwork et al., 2009). Bilateral CSA images of MF were obtained in the transverse plane at vertebral levels L2 to L5 with the muscles relaxed.

Images were stored and later measured offline by a single examiner using ImageJ software 1.36b (http://imagej.nih.gov/ij). Abdominal muscle thickness was measured as the perpendicular distance between the superior and inferior muscle fascias at approximately the middle of the image identified using the software's Cartesian coordinates (Fig. 1A and B) (Hides et al., 2007). MF CSA was measured by tracing the inner edge of the fascial boundaries (Fig. 1C) (Hides et al., 2008a) and thickness measured from the tip of the zygapophyseal joint to the inferior fascial edge of the superior border of the muscle (Fig. 1D) (Wallwork et al., 2007).

3. Statistical analysis

Percentage thickness change was calculated as 100*(thickness of muscle contracted - thickness relaxed)/thickness relaxed. Bland and Altman plots were inspected to identify any systematic patterns in the differences associated with muscle size (Bland and Altman, 1986). Intraclass correlation coefficients were calculated (ICC 3,1) (Shrout and Fleiss, 1979) and classified according to the recommendations of Shrout (Shrout, 1998) (≤0.10 = virtually none, 0.11–0.40 = slight, 0.41–0.60 = fair, 0.61–0.80 = moderate, and 0.81–1.0 = substantial). Standard error of measurement (SEM) (de Vet et al., 2006) and minimal detectable change (MDC) were also calculated. STATA 12 was used for data analysis.

4. Results

Table 1 summarises the characteristics of the reliability study participants and of the other participants in the USI sub-study of the VIDEO trial. The reliability study group included relatively more males, and women who were shorter and lighter than the other women in the USI sub-study.

Other than for the right IO when contracted (ICC 0.75), ICC values for abdominal muscles were substantial (0.87–0.98) (Tables 2 and 3). Other than for IO when contracted (difference 6.5%), the differences between measurements were relatively small (≤3.2%) and considerably smaller than their corresponding MDC values. ICCs were lower, and SEM values higher, for percentage thickness change. Reliability of measurements of right MF thickness (at rest and contracted) was fair to moderate at the L2-L3 and L3-L4 spinal levels (ICC 0.55–0.74) (Table 4) and moderate to substantial at other levels. On average, the test-retest differences were small (≤3%) and considerably smaller than the corresponding MDC. Percentage change thickness was not reliably measured. Reliability of MF CSA measures was substantial (ICC 0.84–0.91) (Table 5), with small test-retest differences that were much smaller than the MDC.

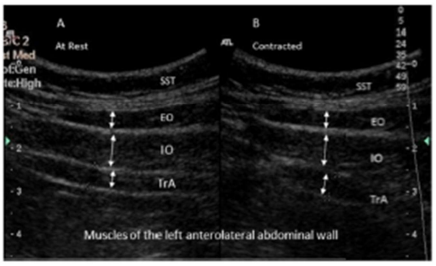
Bland and Altman plots of all muscle measurements revealed no systematic pattern of variability across the range of measurement (data not shown).

5. Discussion

This study reports test-retest reliability of USI and measurement of thickness of abdominal and MF muscles, and MF CSA (L2-L5) in adults aged 50–79 years. Importantly, we assessed test-retest reliability for muscles for which this has not previously been reported in older adults (Cuellar et al., 2016). Reliability was substantial for all measures other than thickness of IO and of MF at L2-L3 and L3-L4 spinal levels, supporting the use of USI as a reliable tool for the assessment of abdominal and MF muscle thickness and MF CSA of older adults for clinical and research purposes.

Age related changes in skeletal muscle such as increased water and fat content and fibrous tissue can increase ultrasound image echogenicity, and could reduce the reliability of muscle measurements in older adults (Stokes et al., 2005, Teyhen et al., 2007).

A



Split-screen image showing the muscles of the left anterolateral abdominal wall at rest (A) and contracted (B). Abbreviations: SST: superficial soft tissue, (EO): external oblique, (IO): internal oblique, (TrA) transversus abdominis.

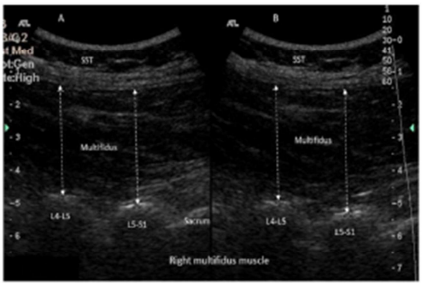
B

Ultrasound image showing the right rectus abdominis muscle. Thickness of the muscle was measured at rest as the perpendicular distance between the superior and inferior hypoechoic muscle fascias at the middle of the image

C

Bilateral image of multifidus in transverse section at the L5 vertebral level. Cross-sectional area (CSA) of the multifidus muscle was measured by tracing around the inner edge of the fascial boundaries of the muscle as shown on the left side of the image. Abbreviations: SST, sub-cutaneous soft tissue

D



Split-screen parasagittal image of the right multifidus muscle at rest (A) and contracted (B). Thickness measurements were made from the tip of the zygapophyseal joint to the inferior fascial edge of the superior border of the muscle. Abbreviations: SST, sub-cutaneous soft tissue

Fig. 1. A. Split-screen image showing the muscles of the left anterolateral abdominal wall at rest (A) and contracted (B). Abbreviations: SST: superficial soft tissue, (EO): external oblique, (IO): internal oblique, (TrA) transversus abdominis. B. Ultrasound image showing the right rectus abdominis muscle. Thickness of the muscle was measured at rest as the perpendicular distance between the superior and inferior hypoechoic muscle fascias at the middle of the image. C. Bilateral image of multifidus in transverse section at the L5 vertebral level. Cross-sectional area (CSA) of the multifidus muscle was measured by tracing around the inner edge of the fascial boundaries of the muscle as shown on the left side of the image. Abbreviations: SST, sub-cutaneous soft tissue. D. Split-screen parasagittal image of the right multifidus muscle at rest (A) and contracted (B). Thickness measurements were made from the tip of the zygapophyseal joint to the inferior fascial edge of the superior border of the muscle. Abbreviations: SST, sub-cutaneous soft tissue.

Table 1
Characteristics of participants in the reliability study and of remaining ultrasound sub-study participants (non-participants).

Characteristic	Reliability study (N = 23)	Non-participants (N = 163)
Age (yrs.)	62.4 (6.3)	64.7 (7.3)
Sex: males, % (n/N)	70 (16/23)	54 (88/163)
Height (cm) (males, females	177.8(6.1), 158.4(6.6)	176.1(6.5), 161.6(6.1)
Weight (kg) (males, females)	88.4(12.6), 68.5(16.0)	91.8(13.6), 78.4(14.7)
BMI (kg/m^2)	29.7 (11.7)	29.8 (4.8)
Low back pain, % (n/N)	39.1 (9/23)	35.6 (58/163)

Results are reported mean (standard deviation) unless otherwise stated. %: percentage; BMI: body mass index.

Despite this and the additional potential for measurement error during the process of taking repeated ultrasound measures, test-retest reliability of abdominal muscle thickness and MF CSA in our study were substantial (ICC = >0.81), and comparable with the reliability of just measuring images of the same muscles in a population-based sample of adults aged 65–89 years (ICC= > 0.85) (Wilson et al., 2016). Furthermore, the test-retest reliability of MF CSA was comparable to that of young adults (ICC = 0.72–0.80) (Frantz Pressler et al., 2006). This suggests that USI test-retest assessment of abdominal and MF muscle thickness at rest and contracted, MF CSA at rest and percentage change in abdominal thickness of older adults can be reliably performed by a trained assessor following a standardised protocol.

The test-retest reliability of measurements of MF muscle thickness in our study ranged from fair to substantial (ICC = 0.55–0.86), being somewhat lower at L2-3 and L3-4 spinal levels. This is lower than previously reported for at L4-L5 in older adults (Sions et al., 2014a,b), which may be in part due to that study

Table 2
Test-retest reliability of measuring right abdominal muscle thickness (cm).

Muscle	N	Test	Retest	Difference	SEM	MDC_{95}	Intraclass correlation	
		Mean (SD)	Mean (SD)	Mean (SD)			ICC(3,1)	95% CI
RA	23	0.86 (0.19)	0.88 (0.19)	−0.016 (0.061)	0.04	0.12	0.95	(0.88, 0.98)
TrA (rest)	23	0.39 (0.10)	0.40 (0.11)	−0.004 (0.034)	0.02	0.07	0.95	(0.88, 0.98)
TrA (contract)	23	0.58 (0.16)	0.59 (0.16)	0.010 (0.004)	0.04	0.10	0.95	(0.89, 0.98)
Thickness change, %	23	50.66 (32.76)	54.35 (38.03)	−3.689 (21.704)	15.35	42.54	0.81	(0.61, 0.92)
IO (rest)	23	0.73 (0.16)	0.75 (0.17)	−0.024 (0.013)	0.05	0.12	0.92	(0.83, 0.97)
IO (contract)	23	0.95 (0.24)	1.01 (0.28)	−0.062 (0.185)	0.13	0.36	0.75	(0.49, 0.89)
Thickness change, %	23	30.54 (22.65)	35.12 (31.71)	−4.580 (32.967)	23.31	64.61	0.28	(−0.14, 0.62)
EO (rest)	23	0.41 (0.10)	0.41 (0.10)	−0.008 (0.031)	0.02	0.06	0.95	(0.89, 0.98)
EO (contract)	23	0.47 (0.99)	0.49 (0.10)	−0.013 (0.052)	0.04	0.10	0.87	(0.71, 0.94)
Thickness change, %	23	19.34 (21.80)	19.84 (19.89)	−0.5 (15.440)	10.92	30.26	0.73	(0.46, 0.87)

Abbreviations: *RA*, rectus abdominis; *EO*, external oblique; *IO*, internal oblique; *TrA*, transversus abdominis; *rest*, resting thickness (cm); *contract*, contracted thickness (cm); *SD*, standard deviation; *SEM*, standard error of measurement; *MDC*, minimal detectable change; *ICC*, intra-class correlation coefficient (95% confidence interval).

Table 3
Test-retest reliability of measuring left abdominal muscle thickness (cm).

Muscle	n	Test	Retest	Difference	SEM	MDC_{95}	Intraclass correlation	
		Mean (SD)	Mean (SD)	Mean (SD)			ICC(3,1)	95% CI
RA	23	0.85 (0.18)	0.86 (0.19)	−0.007 (0.036)	0.03	0.07	0.98	(0.96, 0.99)
TrA (rest)	23	0.37 (0.10)	0.38 (0.10)	−0.000 (0.036)	0.03	0.07	0.93	(0.84, 0.97)
TrA (contract)	23	0.60 (0.15)	0.60 (0.16)	−0.003 (0.049)	0.04	0.10	0.95	(0.87, 0.98)
Thickness change, %	23	63.53 (36.04)	61.77 (28.92)	1.762 (17.916)	12.67	35.11	0.85	(0.68, 0.93)
IO (rest)	23	0.77 (0.19)	0.75 (0.20)	0.024 (0.068)	0.05	0.13	0.94	(0.86, 0.97)
IO (contract)	23	1.06 (0.32)	1.03 (0.33)	0.026 (0.086)	0.06	0.17	0.96	(0.92, 0.99)
Thickness change, %	23	37.08 (22.90)	38.36 (27.19)	−1.287 (15.460)	10.93	30.30	0.81	(0.61, 0.92)
EO (rest)	23	0.42 (0.11)	0.42 (0.09)	0.006 (0.040)	0.03	0.08	0.92	(0.82, 0.97)
EO (contract)	23	0.52 (0.14)	0.52 (0.14)	−0.001 (0.043)	0.03	0.09	0.95	(0.89, 0.98)
Thickness change, %	23	24.07 (27.13)	25.55 (28.95)	−1.477 (16.359)	11.57	32.06	0.83	(0.64, 0.92)

Abbreviations: *RA*, rectus abdominis; *EO*, external oblique; *IO*, internal oblique; *TrA*, transversus abdominis; *rest*, resting thickness (cm); *contract*, contracted thickness (cm), *SD*, standard deviation; *SEM*, standard error of measurement; *MDC*, minimal detectable change; *ICC*, intra-class correlation coefficient (95% confidence interval).

Table 4
Test-retest reliability of right lumbar multifidus muscle thickness measures (cm).

Muscle	n	Test	Retest	Difference	SEM	MDC_{95}	Intraclass correlation	
		Mean (SD)	Mean (SD)	Mean (SD)			ICC(3,1)	95% CI
MF L2-L3 (rest)	23	2.60 (0.30)	2.52 (0.41)	0.078 (0.338)	0.24	0.66	0.55	(0.19, 0.78)
MF L2-L3 (contract)	23	2.83 (0.38)	2.80 (0.43)	0.032 (0.292)	0.21	0.57	0.74	(0.48, 0.88)
Thickness change, %	23	8.95 (10.42)	11.44 (9.20)	−2.491 (11.586)	8.19	22.71	0.30	(−0.11, 0.63)
MF L3-L4 (rest)	23	2.42 (0.33)	2.372 (0.32)	0.044 (0.302)	0.21	0.59	0.57	(0.21, 0.79)
MF L3-L4 (contract)	23	2.66 (0.40)	2.61 (0.33)	0.052 (0.315)	0.22	0.62	0.63	(0.31, 0.83)
Thickness change, %	23	10.58 (11.52)	10.55 (10.10)	0.033 (15.896)	11.24	31.16	−0.08	(−0.47, 0.34)
MF L4-L5 (rest)	23	2.85 (0.48)	2.87 (0.60)	−0.027 (0.315)	0.22	0.62	0.83	(0.64, 0.92)
MF L4-L5 (contract)	23	3.02 (0.52)	3.05 (0.65)	−0.031 (0.313)	0.22	0.61	0.86	(0.69, 0.94)
Thickness change, %	23	6.12 (6.89)	6.28 (8.97)	−0.165 (8.546)	6.04	16.75	0.43	(0.03, 0.71)
MF L5-S1 (rest)	23	2.84 (0.37)	2.86 (0.49)	−0.016 (0.311)	0.22	0.61	0.74	(0.48, 0.88)
MF L5-S1 (contract)	23	3.04 (0.47)	3.09 (0.57)	−0.048 (0.413)	0.29	0.80	0.69	(0.39, 0.86)
Thickness change, %	23	6.90 (6.95)	8.46 (11.36)	−1.561 (12.244)	8.66	24	0.16	(−0.27, 0.53)

Abbreviations: *MF*, lumbar multifidus; *L2 - L5*, lumbar vertebral level; *rest*, resting thickness (cm); *contract*, contracted thickness (cm); *SD*, standard deviation; *SEM*, standard error of measurement; *MDC*, minimal detectable change; *ICC*, intra-class correlation coefficient (95% confidence interval).

using the average of three measurements to calculate ICCs and SEMs. Averaging three measurements improves measurement precision (SEM) by up to 50% (Koppenhaver et al., 2009), but only delivers modest improvements in reliability of MF thickness compared with single measurements (Djordjevic et al., 2014, Wallwork et al., 2007). Potential gains in reliability need to be weighed against the logistical disadvantages (e.g. time) of performing multiple measurements in clinical and research settings.

The reasons for the lower reliability of measuring upper spinal segments in our study are not clear. One contributing factor may be the higher degree of difficulty localising these segments and excluding longitudinal muscle fibres from the erector spinae in the measurement of MF thickness. Although the reasons for the marked side-to-side difference in the reliability of thickness and percentage thickness change of the IO are also unclear, our results are consistent with a previous image reading study confined to lateral abdominals in adults of mean age 72 years (Stetts et al., 2009). It is possible that consistently imaging the right side first created a learning effect that lessened variability in the contraction of the left IO.

Estimates of reliability for percent thickness change were low, particularly those for MF (ICC -0.08–0.43), consistent with previous reports for L4-5 MF thickness (Sions et al., 2014b) and IO. This is not unexpected, as multiple factors influence percentage muscle thickness changes such as resting state, contraction type, and variability in performance of the contraction (Whittaker and

Table 5
Test-retest reliability of lumbar multifidus cross-sectional area measures (cm^2).

Muscle	n	Test	Retest	Difference	SEM	MDC_{95}	Intraclass correlation	
		Mean (SD)	Mean (SD)	Mean (SD)			ICC(3,1)	95% CI
(R) MF L2	23	2.93 (0.46)	3.01 (0.50)	−0.079 (0.271)	0.19	0.29	0.84	(0.66, 0.93)
(L) MF L2	23	2.90 (0.46)	2.94 (0.49)	−0.039 (0.266)	0.19	0.28	0.84	(0.67, 0.93)
(R) MF L3	23	3.78 (0.53)	3.87 (0.57)	−0.088 (0.252)	0.18	0.22	0.90	(0.77, 0.96)
(L) MF L3	23	3.86 (0.58)	3.79 (0.59)	0.067 (0.259)	0.18	0.22	0.90	(0.78, 0.96)
(R) MF L4	23	4.74 (0.60)	4.79 (0.67)	−0.048 (0.274)	0.19	0.23	0.91	(0.80, 0.96)
(L) MF L4	23	4.84 (0.56)	4.82 (0.62)	0.014 (0.293)	0.21	0.27	0.88	(0.74, 0.95)
(R) MF L5	23	5.31 (0.56)	5.39 (0.60)	−0.085 (0.260)	0.18	0.22	0.90	(0.78, 0.96)
(L) MF L5	23	5.39 (0.57)	5.38 (0.56)	0.008 (0.264)	0.19	0.23	0.89	(0.76, 0.95)

Abbreviations: (R), right side; (L), left side; *MF*, lumbar multifidus; *L2 - L5*, lumbar vertebral level; *SD*, standard deviation; *SEM*, standard error of measurement; *MDC*, minimal detectable change; *ICC*, intra-class correlation coefficient (95% confidence interval).

Stokes, 2011). Therefore, current approaches to assessing percentage thickness change of lumbar MF and IO appear insufficiently reliable to measure changes in muscle size over time. Further research could investigate ways to improve the reliability of these measures, possibly through different approaches to standardising the performance of contractions, and alternative approaches that more closely target IO.

6. Study limitations

This study has several limitations. A trained examiner performed USI so the results may not be generalizable to examiners with less training, though MF thickness has been measured with high test-retest reliability in older adults by operators with limited USI training (Sions et al., 2014b). Reliability may have been higher with multiple rather than single measurements, but the reliability we achieved suggests that single measurements can be made with substantial consistency, at least at the lower spinal levels where LBP is more prevalent. Lastly, participants were vitamin D insufficient and so the muscle measures are not normative for the general population.

7. Conclusion

Despite the challenges of imaging older adults using USI, a trained assessor can reliably assess abdominal and MF muscle thickness at rest and contracted, CSA at rest and percentage change in abdominal thickness, but not percentage change in MF thickness, on different days. The substantial reliability of most measures suggest that USI performed by a trained assessor using established protocols is sufficiently reliable to be used in clinical practice and for research in older people.

Author contributions

Study conception and design: TMW, GJ, JAH, CD.
Project management of study during implementation: TMW.
Acquisition of data: WAC.
Design of data analysis plan: WAC, JAH, CLB, TMW.
Analysis and interpretation of data: WAC, JAH, CLB, MLC, TMW.
Drafting and revisions of manuscript: WAC, JAH, CLB, MLC, GJ, TMW, CD.
All authors approved the final version of the manuscript.

Conflicts of interest and sources of funding

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Appendix 13: Vitamin D supplements for trunk muscle morphology in older adults: secondary analysis of a randomized controlled trial

ORIGINAL ARTICLE

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Vitamin D supplements for trunk muscle morphology in older adults: secondary analysis of a randomized controlled trial

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Abstract

Background The effect of vitamin D supplementation on postural muscles of the trunk is of particular interest because low 25-hydroxyvitamin D [25(OH) D] levels are associated with decreased postural balance and increased risk of falls. Understanding the role of vitamin D supplementation plays in trunk muscle function of older adults is necessary, as this is a potentially modifiable factor to improve postural muscle function and decrease the risk of falling of older adults. The objective of this randomized controlled trial was to evaluate the effect of 12 months of vitamin D supplementation compared with placebo, on morphology and function of the trunk muscles of adults aged 50 to 79 years with low serum 25(OH) D levels.

Methods This was a secondary analysis of a randomized, placebo-controlled, and double-blind clinical trial conducted be- tween June 2010 and December 2013 in Tasmania, Australia. The clinical trial was registered with the Australian New Zealand clinical trial registration agency, ClinicalTrials.gov identifier: NCT01176344; Australian New Zealand Clinical Trials Registry: ACTRN 12610000495022. Participants were aged 50–79 years with ongoing symptoms of knee osteoarthritis and with low serum [25(OH) D] (12.5 to 60 nmol/L, 5.2 to 24 ng/mL). Participants were randomly assigned to either monthly 50 000 IU oral vitamin D3 (n = 104) or an identical placebo (n = 113) for 24 months as per clinical trial protocol. The primary outcomes in this pre-specified secondary analysis were between-group differences in change in size of rectus abdominis, transversus abdominis, internal oblique, external oblique, and lumbar multifidus muscles and function (assessed by change in thickness on contraction) of these muscles (excepting rectus abdominis) from baseline to 12 months. Muscle size was assessed using ultrasound imaging.

Results Of 217 participants (mean age 63 years, 48% women), 186 (85.7%) completed the study. There were no significant between-group differences in change in size or function of the abdominal or multifidus muscles after 12 months of vitamin D supplementation.

Conclusions A monthly dose of 50 000 IU of vitamin D3 alone for 12 months does not affect the size or ability to contract trunk muscles of independent community-dwelling older adults with symptomatic knee osteoarthritis and low serum 25(OH) D levels regardless of body mass index status or degree of vitamin D deficiency. An effect of vitamin D supplementation on other aspects of trunk muscle function such as strength, power, or physical function cannot be ruled out.

Keywords Randomized controlled trial; Vitamin D supplementation; Postural trunk muscles; Muscle size and function; Older adults; Ultrasound imaging

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Introduction

Population levels of serum 25-hydroxyvitamin D [25(OH) D] are variable around the world, but deficiency is common in older adults due to decreased sun exposure, decreased pro- duction of vitamin D in the skin, insufficient intake of vitamin D in their diet, and institutionalization.[1–4] Mean population 25(OH) D levels commonly fall below 50 nmol/L (20 ng/mL), which is considered to be the minimum target level for adequate bone health, mineral homeostasis, and muscle function.[4–6]

Common clinical presentations of severe vitamin D deficiency include bone pain, gait disturbances, and muscle weakness, especially of proximal muscles of the upper and lower limbs and muscles of the trunk.[7] Previous research has found that vitamin D plays a vital role in muscle development and growth.[8] The mechanism may be through $1,25(OH)_2$ binding to a specific vitamin D receptor found in skeletal muscle[9,10] leading to de novo protein synthesis and thus muscle cell proliferation and growth.[11,12] Furthermore, a review of randomized controlled trials (RCTs) has examined the effect of vitamin D supplementation on several aspects of muscle function including lower limb strength, handgrip, postural balance, gait speed, and physical performance (timed- up-and-go test).[13] Even though evidence in this review was conflicting, 7 of 11 studies demonstrated beneficial effects, as has another published RCT.[14] A more recent systematic review and meta-analysis of 30 RCTs by Beaudart *et al*.[15] found small but significant positive effects of vitamin D supplementation on lower limb muscle strength, although there were no effects on muscle mass or power. Thus, there is both a biological basis and clinical trial evidence for considering that correcting vitamin D deficiency may improve muscle strength and function.

Muscles of the trunk, particularly the abdominal and lumbar multifidus muscles (MF), are postural muscles tonically active during daily upright activities[16] and essential for the stability of the spine, balance, and posture.[17–19] Trunk muscle size is correlated with strength,[20,21] and among older adults, trunk muscle strength has been found to be associated with mobility and falls.[22,23] The effect of vitamin D supplementation on muscles of the trunk is of particular interest because low 25(OH) D levels are associated with decreased postural balance[13] and increased risk of falls in older adults.[24] Consequently, vitamin D supplementation has the potential to be a relatively cheap intervention to improve postural muscle function and decrease the risk of falling among older adults. Despite this, to our knowledge, the effects of vitamin D supplementation on trunk muscles have not been assessed previously. Therefore, the objective of this RCT was to evaluate the effect of 12 months of vitamin D supplementation compared with placebo, on morphology and function of the trunk muscles of adults aged 50 to 79 years with low serum 25(OH) D levels.

Methods

Trial design

The Vitamin D Effect on Osteoarthritis (VIDEO) study was a randomized, placebo-controlled, and double-blind clinical trial conducted between June 2010 and December 2013, with the main objectives of determining if vitamin D supplementation could reduce knee cartilage volume loss, prevent progression of knee structural abnormalities, improve lower limb muscle strength, and alter the progression of knee pain.[25,26] The protocol for VIDEO and its pre-specified analyses have been published.[25] This pre-specified secondary analysis investigating the effects of vitamin D supplementation on the size of abdominal and lumbar MF muscles over 12 months was undertaken in one of the two VIDEO sites, namely, Hobart, Tasmania, Australia. VIDEO was registered with the Australian New Zealand clinical trial registration agency, ClinicalTrials.gov identifier: NCT01176344; Australian New Zealand Clinical Trials Registry: ACTRN 12610000495022.[25] The clinical trial and sub-studies were conducted following the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and the 2007 Australian National Statement on Ethical Conduct in Human Research.

Participants

Participants were recruited through advertisements in the local media and community groups, and referrals from general practitioners, specialist rheumatologists, and orthopaedic surgeons. Inclusion and exclusion criteria are described in detail in the published clinical trial protocol.[25] In brief, participants were people aged 50–79 years, with on- going symptoms of knee osteoarthritis for at least 6 months with pain levels between 20 and 80 mm on a 100 mm visual analogue scale and serum 25(OH) D levels between 12.5 and 60 nmol/L (5.2 to 24 ng/mL). Exclusion criteria included severe radiographic knee osteoarthritis, severe pain on standing, hypersensitivity to vitamin D, any condition affecting oral drug absorption, and anticipated need for knee or hip surgery within the next 2 years. Ethics approval was received from The Tasmania Health and Human Ethics Committee (reference number H1040). Written informed consent was obtained from all participants.

Randomization and blinding

Participants were randomly assigned to a vitamin D or a placebo group using computer-generated allocation with a 1:1 ratio.

Allocation concealment was ensured by using a central automated process independent of the investigators. Participants, investigators, and research coordinators were all blinded to the treatment allocation. Blinding both for the main study and for the trunk muscle outcomes was maintained until all data were collected, cleaned, and confirmed for accuracy and statistical analyses were completed.

Interventions

Participants in the treatment group were given one 50 000 IU (1.25 mg) vitamin D3 (cholecalciferol) capsule per month, for 24 months. Participants in the control group were given an identical inert placebo. The vitamin D3 compound and inert placebo were acquired from Nationwide Compounding Pharmacy, Melbourne, Australia.[25]

Outcomes

Primary outcome measures in this pre-specified secondary analysis were between-group differences in change in muscle morphology: (i) changes in muscle thickness of the abdominal muscles [rectus abdominis (RA), transversus abdominis (TrA), internal oblique, and external oblique] and the lumbar MF muscles; (ii) changes in cross sectional area (CSA) of the MF muscles; and (iii) changes in muscle thickness with contraction of the abdominal muscles (except RA) and the MF muscles from baseline to 12 months.

Image capture and measurement

Ultrasound muscle images were taken using a Phillips HDI 5000 ultrasound machine (Bothwell, WA, USA) in brightness mode (B-mode) with a handheld 4–7 MHz broadband curved array transducer. Image capture and measurement of the abdominal wall and MF muscles were undertaken following previously published protocols.[27–36] The ultrasound imaging (USI) assessments were conducted by a physical therapist who undertook 36 h of practical training in USI at the beginning of the project.

Muscles of the abdominal wall were imaged in transverse section. Participants were positioned in supine lying, with a pillow under their knees.[30,28] To elicit a voluntary contraction of the abdominal wall, participants were asked to 'take a re- laxed breath in and out, hold your breath out, and then draw in your lower abdomen without moving your spine'.[28] The RA muscles were only imaged at rest, and the transversus abdominis, internal oblique, and external oblique muscles were imaged at rest and on contraction.[30]

Imaging of the lumbar MF muscles was performed with participants positioned in prone lying, with a pillow placed under their abdomen to reduce lumbar lordosis.[31,32,34] Image of the lumbar MF muscles were captured both at rest (in the transverse plane) and during contraction (in the parasagittal plane). Instructions for the isometric contraction were 'take a relaxed breath in and out, hold your breath out and try to slowly "swell" and contract the muscle without moving the spine'.[37]

Ultrasound images were stored and later analysed offline by a single examiner using a software package (Image J Image Processing and Analysis, version IJ 1.46r, http://imagej.nih.gov/ij/). The thickness of the abdominal muscles was measured as the perpendicular distance between the superior and inferior hyperechoic muscle fascias at approximately the middle of the image identified using the software's Cartesian coordinates.[28] The CSA of the MF muscle was measured by tracing around the inner edge of the fascial boundaries of the muscle,[27,31] and the thickness of the MF muscle was measured from the tip of the zygapophyseal joint to the inferior fascial edge of the superior border of the muscle.[34] Intraclass correlation coefficients (ICC) for abdominal and MF muscle measurements were ICC = > 0.85 for interrater USI image measurement reliability[35] and ICC = 0.74–0.98 for test–retest reliability.[36]

Other factors

Height was measured by stadiometer to the nearest 0.1 cm (Leicester Height Measure, Invicta Plastics Ltd, Leicester, UK). Weight was measured by calibrated scales (Heine S-7307, Heine, New Hampshire, USA) and body mass index (BMI) was calculated [weight (kg)/height (m^2)]. Knee pain scores were obtained using a visual analogue pain scale in 100 mm, assessing pain during walking, using stairs, in bed, sitting or lying, and standing. The total pain score was calculated as the sum of the five items (range 0–500).[38] Total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score was calculated as the sum of the scores in each of its subscales that included pain, stiffness, and physical function. Missing data were managed according to the WOMAC user guide.[38] Physical activity was measured using the short version of the International Physical Activity Questionnaire (IPAQ) instrument. Data were collected on vigorous and moderate activity as well as walking and sitting, but data on sitting were not used in the analysis. Total IPAQ scores were calculated according to published guidelines.[39,40] Current low back pain status was assessed by a questionnaire asking 'do you currently have any pain in your back?', and pain scores were obtained using a Visual Analogue Scale (0–100 mm). History of back surgery, abdominal surgery, and medications were obtained by questionnaire. Leg strength measures to the nearest kilogram were obtained for both legs simultaneously using a dynamometer (TTM Muscular Meter, Tokyo, Japan) as described by Scott *et al.*[41] This is an isometric strength muscle

test, predominantly for the quadriceps and hip extensor muscles. Grip strength was assessed with a Hydraulic hand-held dynamometer.

25-Hydroxyvitamin D

Serum 25(OH) D was assayed at screening, 3 and 24 months. Blood samples were centrifuged after standing for 10 min at room temperature and the resultant serum frozen at 80°C until assayed using direct competitive chemiluminescent immunoassays (DiaSorin Inc.). The intraassay and interassay coefficients of variation were 3.2% and 6.0%.[26]

Sample size

Calculations were based on the standard deviations reported by Rankin *et al*.[30] for the thickness of the abdominal muscles and by Wallwork *et al*.[42] for thickness and CSA of the lumbar multifidus. Correlations between measurements and remeasurement of $r = 0.9$ for abdominal muscle thickness, $r = 0.5$ for multifidus thickness, and $r = 0.7$ for multifidus CSA were observed in our reliability study.[36] On that basis, this study of projected size 200 subjects (100 in each arm) would have 80% power to detect between-group differences of 0.02 to 0.05 cm for change in abdominal muscle thickness, 0.20 to 0.21 cm for change in multifidus thickness, and 0.28 to 0.40 cm^2 for change in multifidus CSA.

Statistical analysis

As summary measures of their distributions, means and standard deviations were used for continuous measures, and percentages and frequencies were used for categorical factors. Random intercept linear mixed models were used to estimate the change between baseline and follow-up in both treatment arms, and the difference in change for the treatment groups, in this intention-to-treat analysis. The models included binary terms for side (left or right) in measurements of muscle thickness and CSA and for state (relaxed or contracted) of muscle thickness. Changes in muscle morphology, that is thickness and CSA in the relaxed state, and change in function (assessed by changes in muscle thickness on contraction) were compared for each group of participants. Because there was no statistically significant differences between the two sides for either group, the means of the right and left muscle sizes were used in the analysis. In additional analyses, adjustments were made for age, sex, and BMI (pre-specified in the proto- col) and for additional factors that were potential confounders and for which there was an imbalance between the treatment arms. Only the adjustment for lower limb strength resulted in a marked change in the estimated effect of the intervention (Table 1). To test for interaction by serum 25(OH) D status at baseline, a binary term generated using a serum 25(OH) D cut-point of 25 nmol/L (10 ng/mL) was included as a covariate and as a component of a product term in the regression model. Similarly, testing for interaction by BMI category [normal ($\leq$25 kg/m^2), overweight ($>$25 to $<$30 kg/m^2), and obese ($\geq$30 kg/m^2)] was performed. The step-down procedure of Holm[43] was used to control the family-wise error rate (Table 3). Statistical analyses were performed using Stata (Version 14.0, Stata Corporation, TX, USA), and a two-sided *P*-value of 0.05 was deemed statistical significance.

Table 1 Baseline characteristics of vitamin D and placebo groups

Vitamin D (*N* = 104)		Placebo (*N* = 113)
Male sex: % (n/N)	53 (55/104)	51 (58/113)
Age (years)	63.7 (7.4)	63.0 (7.3)
Weight (kg)	84.4 (15.5)	84.4 (15.1)
Height (cm)	169.1 (10.2)	170.0 (9.7)
BMI (kg/m^2)	29.5 (5.3)	29.5 (4.5)
BMI $\leq$25 kg/m^2: % (n/N)	15 (16/104)	11 (12/113)
BMI $>$25 to $<$30 kg/m^2: % (n/N)	47 (49/104)	43 (49/113)
BMI $\geq$30 kg/m^2: % (n/N)	38 (39/104)	46 (52/113)
25-hydroxyvitamin D (nmol/L)	42.5 (12.0)	43.9 (12.1)
Total knee WOMAC score (0–2400)	576.3 (394.9)	571.7 (373.3)
Pain (0–500)	121.3 (88.3)	122.7 (84.5)
Stiffness (0–200)	52.6 (41.9)	58.1 (40.5)
Function (0–1700)	402.4 (287.0)	390.9 (274.7)
Physical activity—IPAQ score	3628.9 (4762.0)	3057.6 (3054.0)
Current low back pain: % (n/N)	39 (41/104)	34 (38/113)
Current low back pain—VAS score	28.0 (19.3)	28.3 (22.0)
History of low back surgery: % (n/N)	6 (6/104)	11.0 (12/113)
History of abdominal surgery: % (n/N)	55 (57/104)	50 (56/113)
Medication: Statins; % (n/N)	6.7 (7/104)	12.0 (13/113)
Lower limb strength (kg)	67.1 (42.9)	70.0 (44.8)
Grip strength: right (kg)	30.7 (12.3)	30.8 (11.0)
Grip strength: left (kg)	29.7 (12.0)	29.7 (11.1)

All results reported mean (standard deviation) or % (n/N) where indicated. BMI, body mass index; IPAQ, International Physical Activity

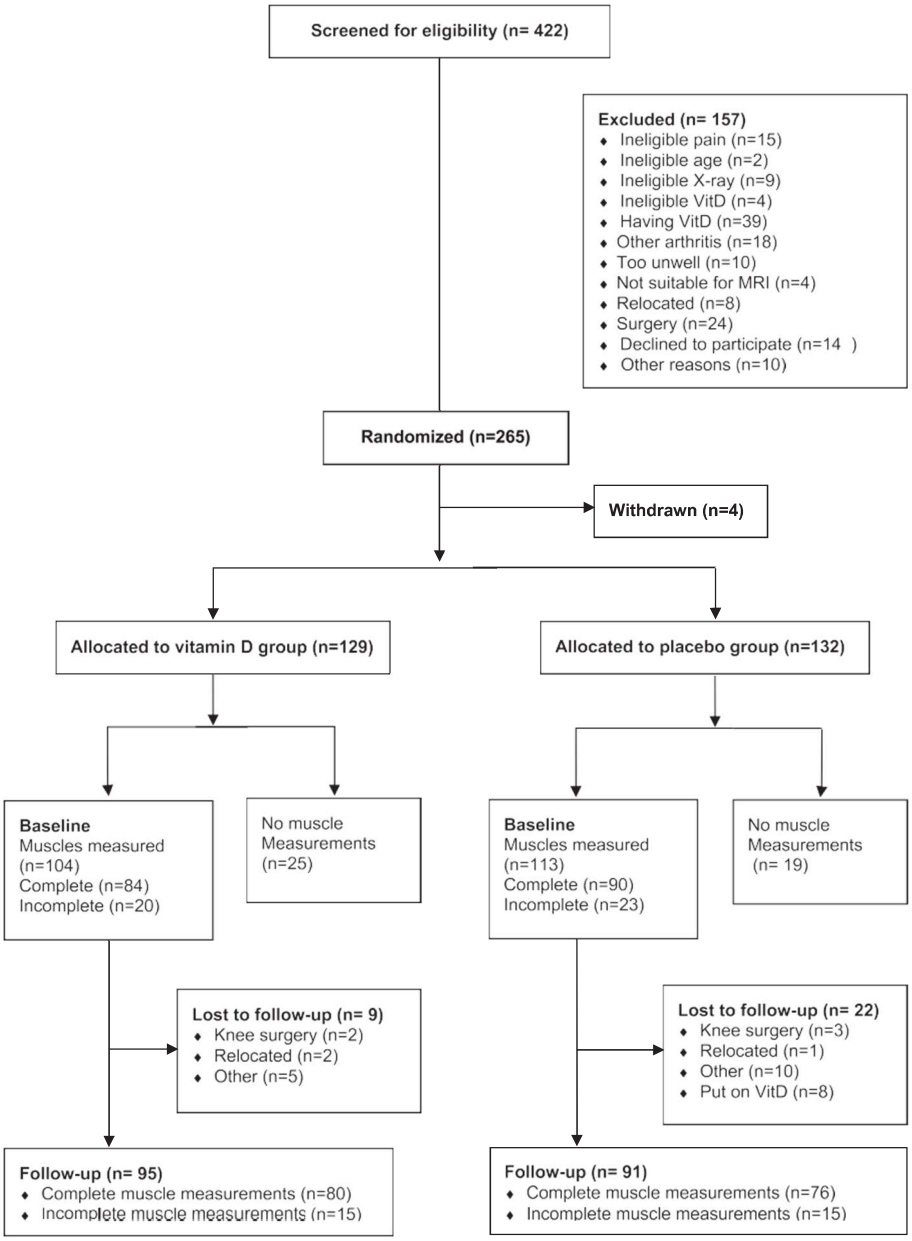
Questionnaire (MET-min/week); VAS, visual analogue scale (0–100 where 0 = no pain and 100 = very worst pain); WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Results

Of the 422 potential VIDEO participants screened at the Hobart site, 265 were randomized and assigned to the treatment or placebo groups. Of these, 104 participants in the treatment group (39.3%) and 113 participants in the placebo group (42.6%) had images of their trunk muscles taken at baseline for this sub-study. Ninety-five and 91 participants had trunk muscle images taken at follow-up 1 year later in the treatment and placebo groups, respectively (Figure 1).

Table 1 summarizes the baseline characteristics of participants in the treatment and placebo groups in this sub-study. The groups were reasonably well matched, with some difference in proportions for gender, low back pain, history of abdominal surgery, statins use, and lower limb strength.

Figure 1 Flowchart of participation.



"Complete" refers to participants with baseline and follow-up data. "Incomplete" refers to participants with baseline data only

Overall knee pain scores measured by the WOMAC were in the low ranges (122/500), while physical activity levels measured by the IPAQ were in the higher ranges (>3000 MET-min/week).[40] Mean serum 25(OH) D levels in the vitamin D group increased by 39.3 nmol/L (15.6 ng/ mL) and 44.5 nmol/L (18.0 ng/mL) at 3 and 24 months respectively, compared with an initial increase of 17.6 nmol/L (7.2 ng/mL) at 3 months and a total increase of 6.8 nmol/L (2.8 ng/mL) at 24 months in the placebo group. There were no baseline differences between the participants in this sub-study and the entire VIDEO cohort (n = 413).[26] The BMI of the study population was relatively high (over 85% were overweight or obese). In the 172 participants of this USI sub-study who had serum 25(OH) D measured at 24 months, increase in serum 25(OH) D levels from baseline to 24 months in overweight (>25 to <30 kg/m^2) and obese participants (≥30 kg/m^2) was 8.7 nmol/L (3.6 ng/mL) and 5.2 nmol/L (2.0 ng/mL) lower, than those participants with normal BMI (≤25 kg/m^2). In fact, 76% of the treatment group achieved serum 25(OH) D levels ≥75 nmol/L (≥30 ng/mL) by 24 months compared with only 7% of the placebo group, the former including 25/33 (76%) of obese and 22/33 (67%) of overweight treatment arm participants.

The between-group treatment effects for trunk muscle size and change in thickness with contraction were small (less than 4% in each muscle), inconsistent in direction, and not statistically significant (Tables 2 and 3). Adjusting for age, sex, and BMI did not change these results (Tables 4 and 5). While additional adjustment for leg strength increased the effect size for multifidus thickness at the L2/L3, L3/L4, and L4/L5 vertebral levels, the only between-group difference that was statistically significant after controlling for family- wise error was at the L2/L3 vertebral level and the effect size (3.5%) remained small (Table 5). Results were similar after further adjustments for statin use, current low back pain, and history of abdominal or back surgery. There were not significant within-group differences in trunk muscle size or function over 12 months in either group. There were no interactions between treatment effect and either baseline 25(OH) D status or BMI in adjusted analyses for any muscle measure (all $P < 0.05$).

Adverse events

A description of adverse events for the full clinical trial has been reported previously.[26] In this sub-study, 44 (42%) out

Table 2 Changes in relaxed abdominal muscle thickness (cm) and in change in muscle thickness with contraction from baseline to follow-up by intervention group

	Vitamin D group			Placebo Group			Between-group differences in change
Muscle	Baseline	Follow-up	Change	Baseline	Follow-up	Change	
RA	0.827 (0.019)	0.845 (0.019)	0.017 (0.008)	0.850 (0.018)	0.860 (0.018)	0.010 (0.008)	0.007 (0.011)
TrA (relaxed)	0.380 (0.011)	0.390 (0.012)	0.011 (0.007)	0.409 (0.011)	0.427 (0.011)	0.018 (0.007)	−0.007 (0.010)
TrA[a]	0.168 (0.009)	0.187 (0.009)	0.018 (0.008)*	0.153 (0.008)	0.176 (0.009)	0.023 (0.009)*	−0.005 (0.012)
IO (relaxed)	0.775 (0.024)	0.752 (0.025)	−0.023 (0.015)	0.851 (0.023)	0.845 (0.024)	−0.006 (0.015)	−0.017 (0.021)
IO[a]	0.221 (0.019)	0.243 (0.019)	0.015 (0.016)	0.203 (0.018)	0.243 (0.019)	0.039 (0.016)*	−0.024 (0.022)
EO (relaxed)	0.431 (0.013)	0.432 (0.013)	0.001 (0.008)	0.451 (0.012)	0.462 (0.013)	0.011 (0.008)	−0.010 (0.011)
EO[a]	0.075 (0.009)	0.091 (0.010)	0.016 (0.010)	0.085 (0.009)	0.093 (0.010)	0.009 (0.010)	0.007 (0.014)

All measures are in cm and are reported as mean (standard error). EO, external oblique; IO, internal oblique; RA, rectus abdominis; TrA, transversus abdominis.
[a]Absolute change in muscle thickness with contraction, calculated as (thickness when contracted – thickness when relaxed).
*Statistically significant $P < 0.05$

Table 3 Between-group differences in changes in relaxed abdominal muscle thickness (cm) and in change in muscle thickness with contraction from baseline to follow-up with and without adjustment for relevant factors

		Adjusted for	
Muscle	Unadjusted model	Age + Sex + BMI	Age + Sex + BMI + Leg strength
RA	0.007 (−0.015, 0.029)	0.010 (−0.012, 0.032)	0.009 (−0.015, 0.032)
TrA (relaxed)	−0.007 (−0.027, 0.013)	−0.004 (−0.024, 0.016)	−0.007 (−0.029, 0.014)
TrA[a]	−0.005 (−0.028, 0.019)	−0.004 (−0.028, 0.019)	−0.004 (−0.030, 0.021)
IO (relaxed)	−0.017 (−0.058, 0.024)	−0.013 (−0.054, 0.028)	−0.010 (−0.054, 0.034)
IO[a]	−0.024 (−0.068, 0.020)	−0.022 (−0.066, 0.022)	−0.021 (−0.069, 0.026)
EO (relaxed)	−0.010 (−0.032, 0.126)	−0.008 (−0.030, 0.015)	−0.010 (−0.034, 0.013)

All measures are in cm and are reported as mean (confident interval). EO, external oblique; IO, internal oblique; RA, rectus abdominis; TrA, transversus abdominis.

[a]Absolute change in muscle thickness with contraction calculated as (thickness when contracted – thickness when relaxed).
*Statistically significant $P < 0.05$.

Table 4 Changes in relaxed multifidus muscle thickness (cm), changes in muscle thickness with contraction, and in changes cross sectional area (cm^2) from baseline to follow-up by intervention group

Vitamin D group differences				Placebo group			Between-group
Muscle	Baseline	Follow-up	Change	Baseline	Follow-up	Change	in change
Muscle thickness							
L2/L3_MF (relaxed)	2.646 (0.046)	2.649 (0.047)	0.003 (0.043)	2.670 (0.044)	2.580 (0.047)	−0.090 (0.043)	0.092 (0.060)
L2/L3_MF[a]	0.140 (0.018)	0.115 (0.018)	−0.025 (0.019)	0.167 (0.017)	0.142 (0.018)	−0.025 (0.019)	0.000 (0.026)
L3/L4_MF (relaxed)	2.331 (0.043)	2.428 (0.044)	0.097 (0.036)*	2.339 (0.041)	2.409 (0.043)	0.070 (0.036)	0.027 (0.051)
L3/L4_[a]	0.134 (0.018)	0.129 (0.018)	−0.005 (0.021)	0.145 (0.017)	0.124 (0.018)	0.020 (0.021)	0.015 (0.029)
L4/L5_MF (relaxed)	2.864 (0.048)	2.817 (0.049)	−0.047 (0.045)	2.913 (0.046)	2.842 (0.049)	0.071 (0.046)	0.024 (0.064)
L4/L5_MF[a]	0.168 (0.018)	0.160 (0.019)	−0.008 (0.019)	0.184 (0.018)	0.180 (0.019)	−0.005 (0.019)	0.003 (0.027)
L5/S1_MF (relaxed)	2.744 (0.049)	2.863 (0.051)	0.119 (0.044)*	2.758 (0.047)	2.925 (0.050)	0.167 (0.045)*	−0.048 (0.063)
L5/S1_MF[a]	0.138 (0.019)	0.153 (0.020)	0.015 (0.021)	0.170 (0.018)	0.178 (0.020)	0.008 (0.021)	0.007 (0.030)
Cross sectional area							
L2_MF_CSA	2.670 (0.054)	2.858 (0.055)	0.188 (0.027)	2.654 (0.052)	2.908 (0.053)	0.254 (0.027)	−0.066 (0.038)
L3_MF_CSA	3.500 (0.061)	3.830 (0.062)	0.330 (0.037)	3.423 (0.058)	3.774 (0.060)	0.350 (0.038)	−0.021 (0.053)
L4_MF_CSA	4.416 (0.068)	4.831 (0.069)	0.415 (0.038)	4.230 (0.065)	4.708 (0.067)	0.478 (0.039)	−0.063 (0.054)
L5_MF_CSA	5.211 (0.081)	5.519 (0.082)	0.307 (0.048)	4.979 (0.077)	5.399 (0.080)	0.420 (0.049)	−0.112 (0.068)

All measures are in cm and are reported as mean (standard error). CSA, cross sectional area; MF, multifidus muscle.
[a]Absolute change in muscle thickness with contraction calculated as (thickness when contracted – thickness when relaxed).
*Statistically significant $P < 0.05$.

Table 5 Between-group differences in change in relaxed multifidus muscle thickness (cm) and in change in muscle thickness with contraction and cross sectional area (cm^2) from baseline to follow-up with and without adjustment for relevant factors

		Adjusted for	
Muscle	Unadjusted model	Age + Sex + BMI	Age + Sex + BMI + Leg strength
Muscle thickness			
L2/L3_MF (relaxed)	0.092 (0.026, 0.211)	0.115 (0.004, 0.234)	0.172 (0.048, 0.296)*
L2/L3_MF[a]	0.000 (0.052, 0.051)	0.115 (0.054, 0.051)	0.176 (0.073, 0.037)
L3/L4_MF (relaxed)	0.027 (0.073, 0.127)	0.038 (0.063, 0.139)	0.054 (0.052, 0.161)
L3/L4_MF[a]	0.015 (0.042, 0.072)	0.017 (0.041, 0.074)	0.001 (0.062, 0.060)
L4/L5_MF (relaxed)	0.024 (−0.102, 0.150)	0.050 (−0.076, 0.176)	0.089 (0.045, 0.222)
L4/L5_MF[a]	−0.003 (−0.056, 0.050)	0.003 (−0.049, 0.056)	0.025 (−0.054, 0.059)
L5/S1_MF (relaxed)	−0.048 (−0.172, 0.076)	−0.028 (−0.152, 0.096)	−0.015 (−0.146, 0.117)
L5/S1_MF[a]	0.007 (−0.052, 0.066)	0.015 (−0.043, 0.073)	0.017 (0.044, 0.078)
Cross sectional area			
L2_MF_CSA	−0.066 (−0.142, 0.009)	−0.059 (−0.135, 0.017)	−0.060 (−0.140, 0.020)
L3_MF_CSA	−0.021 (−0.125, 0.083)	−0.016 (−0.120, 0.089)	0.039 (−0.069, 0.147)
L4_MF_CSA	−0.063 (−0.169, 0.043)	−0.062 (−0.168, 0.045)	−0.041 (−0.148, 0.067)
L5_MF_CSA	−0.112 (−0.246, 0.022)	−0.129 (−0.260, 0.003)	−0.120 (−0.259, 0.019)

All measures are in cm, and are reported as mean (standard error). CSA, cross sectional area; MF, multifidus muscle.
[a]Absolute change in muscle thickness with contraction calculated as (thickness when contracted – thickness when relaxed).
*Statistically significant $P < 0.05$.

of 104 participants in the vitamin D group reported adverse events compared with 30 (27%) out of 113 participants in the placebo group (Table 6). Two cases of hypercalcemia were reported in each group. One instance of hyperthyroid- ism and two episodes of renal calculus were reported in the vitamin D group.[26]

Discussion

To our knowledge, this is the first RCT investigating the effect of vitamin D supplementation on the morphology of key postural trunk muscles of older adults. Apart from the thickness of the MF muscles at the L2–L3 vertebral level, there were no statistically significant differences in change in muscle thickness or CSA between the vitamin D and placebo groups, and all effect sizes were small and not clinically significant. The results suggest that vitamin D supplementation alone is not an effective means to improve or maintain trunk muscle size over time for adults aged 50–79 years, even for those individuals with moderate to severe deficiency.

The purpose of this study was to determine whether vitamin D supplementation alone had beneficial effects in maintaining or improving trunk muscle size and function. In the present study, the within-group changes in trunk muscle size and function over time were all very small. Despite there

Table 6 Adverse events

	Vitamin D No. of participants	(*N* = 104) (%)	Placebo No. of participants	(*N* = 113) (%)
Serious adverse events				
Death	1	(1.0)	0	(0.0)
Malignancy	2	(1.9)	2	(1.8)
Coronary artery disease	1	(1.0)	1	(0.9)
Severe infection	0	(0.0)	1	(0.9)
Major depression	1	(1.0)	0	(0.0)
Nephrolithiasis	1	(1.0)	1	(0.9)
Hospitalization	1	(1.0)	0	(0.0)
Adverse events				
Hypercalcaemia	2	(1.9)	2	(1.8)
Hyperparathyroidism	1	(1.0)	0	(0.0)
Renal	2	(1.9)	0	(0.0)
Falls	2	(1.9)	0	(0.0)
Musculoskeletal	1	(1.0)	1	(0.9)
Neurological	1	(1.0)	1	(0.9)
Gastrointestinal	1	(1.0)	3	(2.7)
Respiratory	2	(1.9)	1	(0.9)
Ocular	1	(1.0)	1	(0.9)
Infection	4	(3.9)	2	(1.8)
Cardiac arrhythmia	1	(1.0)	0	(0.0)
Chest pain	4	(3.9)	4	(3.5)
Pain	6	(5.8)	2	(1.8)
Allergy/immunology	0	(0.0)	2	(1.8)
Other events[a]	9	(8.7)	6	(5.3)

[a]Including headache, lethargy, flu symptoms, and other events.

being plausible reasons to hypothesize that vitamin D supplementation could improve trunk muscle size, our results suggest that increases or maintenance of muscle size or function of older adults cannot be expected from vitamin D supplementation alone, at least over the limited timeframe of 1 year. In peripheral muscles, two systematic reviews reported positive effects of vitamin D supplementation on muscle strength in older adults with baseline 25(OH) D < 30 nmol/L (<12 ng/mL).[15,44] However, in our study of trunk muscles, the response to supplementation did not vary between people with moderate to severe deficiency 25(OH) D (<25 nmol/L, <10 ng/mL) at baseline and those with 25(OH) D levels above this level. Thus, even in people with this degree of deficiency, vitamin D supplementation does not improve trunk muscle size or muscle function as assessed by change in muscle thickness during submaximal contraction.

While there is no consensus on the amount of variation in trunk muscle size required to ascertain clinically meaningful changes in these muscles,[30] previous studies investigating the effect of exercise programmes on trunk muscles in people with low back pain have found interventions that increased muscle size were associated with decreases in pain.[37,45,46] The changes in muscle sizes observed in those studies were larger than those seen in our study, for example, being over 5% for measures of the multifidus and transversus abdominis muscles at rest.[37,45] Thus, exercise programmes or a combination of exercise and functional activities that target trunk muscles may be more effective in improving these muscles than vitamin D supplementation alone.

The effects of vitamin D supplementation on peripheral muscle strength, mass, and power have been examined in a systematic review and meta-analysis.[15] The studies in this review administered a wide range of vitamin D doses (as low 300 IU/day, up to intermittent doses equivalent to around 8600 IU/day). For muscle strength, there was a small but statistically significant positive effect of vitamin D supplementation on lower limb muscle strength [19 studies in 2349 people; vitamin D dose range 400–8600 IU; standard mean difference = 0.19 (95% CI 0.05–0.34)]. However, there was no statistically significant effect of vitamin D supplementation neither on grip strength (16 studies, doses 400–8600 IU/day) nor on muscle mass (six studies, *n* = 538, doses 300–4000 IU/day) or power (five studies, *n* = 245, doses 400–4000 IU/day). The latter is consistent with the lack of effect on muscle size observed in the current study, but as trunk muscle strength and power were not measured in our study it remains to be determined whether vitamin D supplements affect strength or power in trunk muscles.

Previous studies have reported improvements in measures of functional mobility (walking test and 'timed up and go' test) and reduced risk of falls with vitamin D supplementation of older adults.[47,24] Although the present study did not investigate the effect of vitamin D supplementation on falls or functional

mobility, our results suggest that changes to these outcomes are not mediated by trunk muscle size. The effect of vitamin D supplementation on other aspects of trunk muscle function such as strength cannot be ruled out and should be the focus of future research.

Strengths and limitations

The strength of the current investigation is its design. It is a double-blind RCT, which provides robust evidence regarding the efficacy of vitamin D supplementation for improving trunk muscle size. Participants in this study were community-dwelling adults with low serum 25(OH) D. This is the sub-population most likely to benefit from vitamin D supplementation.

It has limitations nevertheless. While the use of random allocation helps to reduce the possibility of imbalance between the treatment arms, in this case randomization did not produce exact balance. However, we collected information that made it possible to adjust for these factors, and the results of the adjusted analyses did not alter the overall conclusions of the study. While the study sample was on average only mildly deficient, there was no interaction between treatment response and vitamin D status at baseline, suggesting that the results are generalizable to both mildly and moderately deficient people. While our sample size was modest, we powered the study appropriately to detect treatment effects that were likely to be clinically meaningful based on existing literature.[37,45,48] We are therefore unlikely to have failed to detect any clinically important treatment effects. The majority of participants were either overweight or obese, which could have influenced their serum 25(OH) D response to supplementation. However, participants with high BMI still achieved large increases in 25(OH) D and a much higher proportion of these participants reached levels ≥75 nmol/L (≥30 ng/mL) than in the placebo group. Furthermore, there was no interaction between treatment response and BMI, so the impact of being an obese population on our results was minimal. The lack of any interaction also suggests that our results are generalizable to people with osteoarthritis who are of normal weight. It is possible that mobility restrictions from knee osteoarthritis may have affected participants' ability to improve trunk muscle size. Nevertheless, levels of knee pain in the study were relatively low, functional limitations were modest, and physical activity levels were reasonable, which makes this scenario unlikely. We used a DiaSorin immunoassay method to measure serum 25(OH) D, rather than mass spectrometry which is considered the gold standard. However, mass spectrometry is not readily avail- able in clinical practice, which would affect translation into practice, and a recent study found that the DiaSorin immuno- assay achieved acceptable performance when compared with mass spectrometry.[49] Our only measure of muscle function was change in muscle thickness with contraction, so we cannot rule out effects of vitamin D supplementation on other aspects of muscle function such as strength, power, physical function, or falls.

Conclusions

There is no evidence that a monthly dose of 50 000 IU of vitamin D3 alone has an effect on the size or ability to contract trunk muscles of independent community-dwelling older adults with symptomatic knee osteoarthritis and low serum 25(OH) D levels regardless of BMI status or degree of vitamin D deficiency. An effect of vitamin D supplementation on other aspects of trunk muscle function such as strength, power, or physical function cannot be ruled out.

Author contributions

T.M.W., G.J., J.A.H., C.D., F.C., and A.W. were responsible for the conception and design of the study. Project management of study during implementation were carried out by T.M.W., C.D., and G.J.; W.A.C. was in charge of data acquisition. Design of data analysis plan were the responsibility of W.A. C., L.B., J.A.H., M.L.C., and T.M.W. Analysis and interpretation of data were performed by W.A.C., L.B., J.A.H., M.L.C., and T.
M.W. Drafting and revisions of manuscript were carried out by W.A.C., L.B., J.A.H., M.L.C., G.J., T.M.W., C.D., F.C., and A.
W. All authors approved the final version of the manuscript.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflicts of Interest

All authors declare no conflict of interest.

Trial registration

ClinicalTrials.gov identifier: NCT01176344; Australian New Zealand Clinical Trials Registry: ACTRN12610000495022. (Data S1).

Data S1. Supporting information

Protocol

Cao Y, Jones G, Cicuttini F, *et al*. Vitamin D supplementation in the management of knee osteoarthritis: study protocol for a randomized controlled trial. Trials 2012;13:131. (Data S1).

Authorship statement

The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia, and Muscle.[50]

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Appendix 14: Body Bequest Program – Registration form

BODY BEQUEST PROGRAM
University of Tasmania
Private Bag 34, Hobart, TAS 7001
Telephone 1800 792 661 (Free call)

UNIVERSITY of TASMANIA

Initial

Body Bequest Program Registration

The following personal information is required by the Registrar of Births, Deaths and Marriages. It is not used to contact any person except the nominated next of kin or Executor (back of form).

NOTE: If you wish to withdraw your bequest or if any of the following information changes please advise the Body Bequest Program at the College of Health and Medicine.

Mr Mrs ……..
Ms Miss **SURNAME** **GIVEN NAMES**

Present address ……..

……..… **Phone number**

Date of Birth **Place of birth**

If born overseas, year of entry into Australia **Religion**

Retired? Yes / No **Occupation** (before retirement / current)

Father's full name

Mother's full maiden name

Details of marriage/s (even i

Where married (town / country)	full date of marriage	Age	Partner's full name (before marriage)
1.	…../…./…..		
2.	…../…./…..		
3.	…../…./…..		
4.	…../…./…..		

Children from all relationships (including legally adopted* and deceased children)

Given Names	*If adopted write (A) after name	Date of Birth	Given Names	*If adopted write (A) after name	Date of Birth

	or 'Deceased'		or 'Deceased'
1.	…../…./…..	5.	…../…./…..
2.	…../…./…..	6.	…../…./…..
3.	…../…./…..	7.	…../…./…..
4.	…../…./…..	8.	…../…./…..

Name and address of your Regular doctor	

THE BACK OF THIS FORM MUST BE READ AND SIGNED

Please provide details of your next of kin (or executor) who will be able to give any additional information at the time of death for registration purposes and who will be notified after the cremation has been completed.

Name: ……. Relationship: ……..
Address: ……
……. Telephone: ……..

I give permission for any of my remains to be retained by the University of Tasmania:

(Please tick ONE (1) box only)

Indefinitely ☐ 5 years ☐ other (not less than 3 years) ☐

☐ I consent to the use of images of my body or parts of my body for education, training or research purposes.
I understand that these images will not be identifiable.

PLEASE READ CAREFULLY BEFORE YOU SIGN

1. It is important that you discuss your intentions with your family so that your wishes may be followed. If the next of kin of the deceased are unhappy regarding the bequest to the University, the College of Health and Medicine may be unable to accept your bequest.

2. If hospitalised, please ensure that the doctor and medical staff are aware of your wish to bequest your body to the University so that in the event of your death they can contact the Body Bequest Program without delay.

3. Unless the circumstances at the time of death compel the University to decline your offer, the College of Health and Medicine will make arrangements and meet expenses in connection with the removal and transport and eventual cremation of your body. The College may retain your body for 5 years unless otherwise specified above.

4. **The University reserves the right to decline acceptance, for any reason, of your body after death***. If the University declines to accept your body, it will not be responsible in any way for your funeral arrangements or associated costs. Consequently, you and your family are strongly advised to agree on alternative arrangements in the event that your body is unable to be accepted at your time of death.

* Some reasons why the University is unable to accept a body are: body subjected to a post mortem examination, the possible existence of a contagious disease, or any other medical grounds, or non-medical grounds, e.g. if the body is not received within four days of the death or if the storage facility is full.

This is to acknowledge that I have read the above information and, having done so, confirm that it is my wish that my body, after death, be made available to the College of Health and Medicine, University of Tasmania, under the provision of the Anatomical Examinations Act 2006, to be used in whatever way shall be deemed most beneficial for the advancement of medical studies and education. I also hereby authorise the University of Tasmania to have full access to my medical records and to make copies of these records when necessary. I understand that the University reserves the right to decline acceptance of my bequest.

Donor's signature: ……..…….…..….. Date: …….

Senior Next of Kin / Executor signature: ……..…….. Date: …….

Witness' signature: ……..…….…..….. Date: …….

NOTES FOR PERSON IN ATTENDANCE AT TIME OF DEATH

Before making any other arrangements please contact the University's Body Bequest Program as soon as possible, but definitely **within 4 days of the death** on 1800 792 661 (9 am – 7 pm, 7 days a week).
In the event of acceptance of the body the Coordinator will make all the necessary arrangements for removal and transportation of the deceased to the College of Health and Medicine and for the registration of the death.

Appendix 15: Ethics – letter of approval to reproduce photographs of cadavers

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone +61 3 6226 7479
Facsimile +61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

30 August 2018

Professor Tania Winzenberg
C/- Menzies Institute for Medical Research

Sent via email

Dear Professor Winzenberg

REF NO: H0017462
TITLE: Dissection photographs and/or drawings from dissection photographs of abdominal and lumbar multifidus muscles for PhD thesis

Document	*Version*	*Date*
Low Risk Application Form		
Information Brochure		
Registration form		

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **07 August 2018** to be conducted at the following site(s):

Menzies Institute for Medical Research

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must

include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.utas.edu.au/research-admin/research-integrity-and-ethics-unit-rieu/human-ethics/human-research-ethics-review-process/health-and-medical-hrec/managing-your-approved-project

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for four years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 30 August 2019. You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Allin Ding
Administration Officer

Appendix 16: PROSPERO – email correspondence regarding systematic review registration

From: jimmy.christie@york.ac.uk [mailto:jimmy.christie@york.ac.uk] **On Behalf Of** CRD Register

Sent: Wednesday, 4 March 2015 8:41 PM

To: William Cuellar

Subject: Re: Enquiry re: retrospective systematic review registration

Hi William,

I'm afraid that it would not be possible for me to accept a completed review retrospectively as to do so would be to leave myself open to appeals from the many authors who have had reviews rejected for similar reasons.

However, if you were to submit the review you would receive an e-mail from me saying that it had been rejected and giving the reason. We have found that publishers are usually quite happy to accept this e-mail as proof of your intent to register the review.

Hope this helps.

Jimmy Christie

From: CRD-REGISTER [mailto:crd-register@york.ac.uk]

Sent: Wednesday, 13 May 2015 5:29 PM

To: William Cuellar

Subject: PROSPERO Registration message [20511]

Dear Mr Cuellar

Thank you for submitting details of your systematic review *Abdominal and multifidus muscles and their role in physical function in older adults: a systematic review* to the PROSPERO register.

We regret that from the information you have provided, we have assessed that your review does not meet the current inclusion criteria for PROSPERO. Reviews that have progressed beyond the point of completing data extraction are not eligible for inclusion in PROSPERO. The aim of the register is to capture information at the protocol stage of a review. Full details of the scope of the register can be found in the About pages at http://www.crd.york.ac.uk/PROSPERO.

We hope that this will not discourage you from registering your next systematic review at the protocol stage, with PROSPERO.

Comments and feedback on your experience of registering with PROSPERO are welcome at crd-register@york.ac.uk

Yours sincerely

James Christie

PROSPERO Administrator
Centre for Reviews and Dissemination
University of York
York YO10 5DD
t: +44 (0) 1904 321040
f: +44 (0) 1904 321041
e: CRD-register@york.ac.uk
www.york.ac.uk/inst/crd

CRD is part of the National Institute for Health Research and is a department of the University of York.